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A TEXT-BOOK

OF

PATHOLOGY

FOR STUDENTS OF MEDICINE

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SECOND EDITION, REVISED AND ENLARGED

ILLUSTRATED; WITH 395 ENGRAVINGS AND 13 COLORED PLATES

TO

THE MEMORY

OF

WYATT JOHNSTON

PREFACE TO SECOND EDITION

The first edition of this work, though not by any means an abbreviation or epitome of the two volumes entitled *Principles of Pathology,* almost necessarily followed the same general lines of presentation. Both works, in short, reflect the arrangement which the subject naturally assumed in the minds of the authors after years of study and considerable experience in teaching. Logically the resultant should afford the simplest and most natural presentation for other minds to grasp. The subject, however, is vast and complicated, and no book can do more than to aid the student in his earnest efforts. That this *Text-book* has measurably succeeded in its purpose is inferrible from the early exhaustion of the large first edition.

In any department of science the multitude of observable facts quickly overwhelms the mental capacity of the beginner. Hence it becomes the instructor's duty to classify and correlate them for the student's easier comprehension, and eventually to teach him to apply the same principles in his independent observations of the concrete. Ability to recognize individual pathological phenomena is of prime importance, but the power to grasp the meaning of the general laws according to which tissues act and react is paramount.

In this the second edition of our text-book the reader will find that continued emphasis is placed upon the reasons underlying pathological conditions; although we trust the facts themselves have not been neglected. Careful attention has been given, in the revision of each subject, that it should include all reliable advances that the past two years have brought forth. A new chapter on "The More Important Infections and Their Prominent Features," has been inserted. In this we have attempted to marshal under one head information that in the previous edition was widely scattered, together with the addition of necessary new material.

We have endeavored to simplify the classification of tumors, to substitute in some degree the term "hyperblastosis" for the less clear "blastomatoid," to indicate the scope of recent work dealing

with toxins and the effects of "split products" in causing disease; a syllabus is placed at the beginning of each chapter detailing its contents with page references; the chapter upon "Monstrosities and Abnormalities" has been relegated to an appendix; ninety-one engravings and two colored plates have been added, and the volume is completely cross-indexed.

Our thanks are due to our former colleagues, Prof. Oskar Klotz, of Pittsburgh, and Prof. S. Burt Wolbach, of Harvard; to our present colleagues, Prof. J. L. Todd, Prof. L. Rhea, and Dr. Maude Abbott, curator of the McGill Pathological Museum, for illustrations and assistance, as well as to those who have favored us with many helpful suggestions.

<div style="text-align: right">J. G. A.
J. McC.</div>

Montreal, 1914.

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A TEXT-BOOK OF PATHOLOGY

PART I

GENERAL PATHOLOGY

CHAPTER I

INTRODUCTORY: CELLS AND TISSUES

THE HISTOLOGY OF THE CELL

THE human body is made up wholly of cells and the products of cells; it takes origin from a cell, and carries on its life by cell activity; even its food is not available for its use save by the intermediation of cells. It is, therefore, reasonable that in seeking to understand the diseases of the human body one should study the diseases of the individual cell. This was realized by the great German pathologist, Virchow, in the middle of last century and, thanks to his influence the pathology of today is a cellular **pathology, is based, that is, upon a study of the disturbances affecting the individual cell.** But to understand these disturbances and their significance it is absolutely essential in the first place to be familiar with the healthy cell and its properties. It might be urged that such a familiarity on the part of the medical student should be taken for granted. Unfortunately there are certain properties of the cell of first importance for the pathologist which receive

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little attention ordinarily from the histologist and biologist; these have to be brought forward in their proper relationship. This first chapter, therefore, is devoted to the properties of the cell, and attempts to show how it is constituted, how cell interacts on cell, how a community reacts upon community—in short, how the cell is at once a unit and a necessary part of a great aggregation of units. If the cell be regarded as an individual, it will be seen that, like a human being, it is born, grows, eats, casts out excretion, rests, is active, becomes useful, learns the work it is destined to do, fills its place in the community, falls sick, recovers, meets with accidents, is set upon by enemies in the shape of infections, enemies which it conquers or by which it is overcome, grows old, dies, and has its place taken by another like it. So far there is a parallel between a man and a cell; and it may be carried farther. The statement is made upon good authority that no man liveth unto himself, because a man's deeds react not only upon himself but upon others, in however indirect a way; so the cell, as part of a community (the organ), cannot withdraw itself from communication with its fellows, but must bear its share of the labor of the organ, and its ill or well-being will react upon the cells that are near it or that depend in any way upon it.

The Constituents of the Cell.—The animal cell consists of two main parts, the **nucleus** and the **cell body,** and even if it cannot be agreed that there is, in all animal and vegetable cells, a nucleus in definite form, we can at least say that there is nuclear and cytoplasmic material. In the cells of man the nucleus has a definite form, generally round or oval; a nuclear membrane can frequently be made out, and inside this the substance shows an alveolar or netted arrangement. The nuclear matter can be demonstrated to consist of (1) the **linin** or achromatic (non-staining) network in which is deposited (2) the **chromatin**—the material which is stainable by nuclear dyes. In the spaces is (3) the **nuclear fluid.** Not always distinguishable are the following: (a) The *nucleolus*, (Fig. 1, *b*), an accumulation of nuclear material which stains differently to the nucleus at large, and is presumed to be of a different, or at least temporarily different, composition; (b) *vacuoles*, which are rare, but may be seen in the nuclei of fat cells (see Fig. 2) and (c) *crystals*. The last two are products of the activity of nuclear metabolism.

The type cell has but a single nucleus; but at times two or many nuclei may be present, a condition which may be due, on the one hand, to division of the nucleus with failure of the cytoplasm to divide, or, on the other, to fusion of separate cells. Both processes evidently occur, as will be discussed when dealing with giant cells.

Although we say that the nuclear material is confined to the nucleus proper, it must be realized that **there is a constant interchange of material between nucleus and cytoplasm.** Many of the granules or formed bodies seen in the cytoplasm, such as the **Nissl** or **tigroid** bodies of the neurocyte or nerve cell (Fig. 1, *c*), are now recognized as of

chromidial nature. By **chromidia** we mean extrusions of chromatin from the nucleus, which undergo modification through interactions with cytoplasmic substances.

Fig. 1
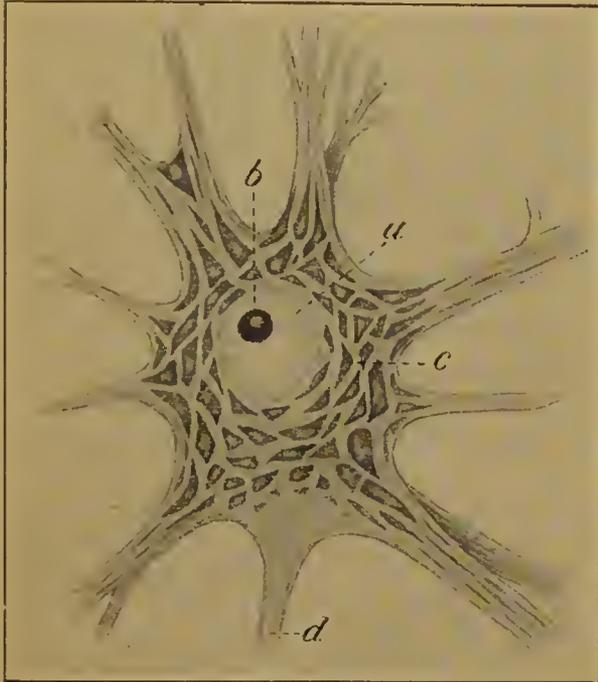
Fig. 2

Motor nerve cell from ventral horn of spinal cord of rabbit. *a*, nucleus; *b*, nucleolus. The angular and spindle-shaped Nissl's bodies of chromidial nature (*c*) are well shown; *d*, axone.
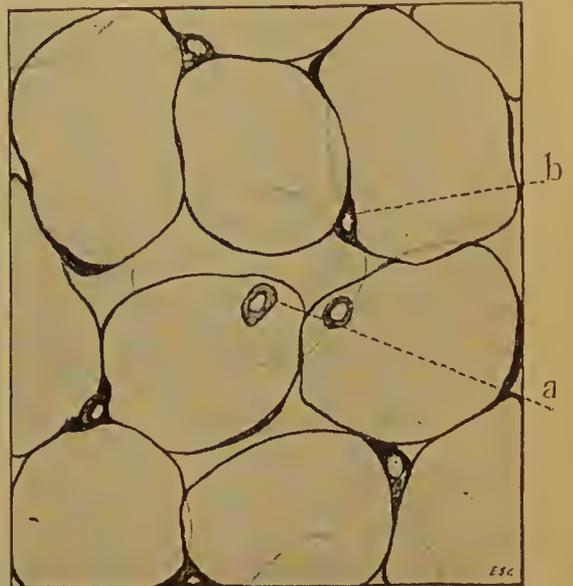
Vacuolation of nuclei of fat cells. Fat cells of retroperitoneal tissue stained by hematoxylin, and examined under the high power, to show the nuclear vacuoles, characteristic of this order of cell. *a*, nucleus seen from above; *b*, seen in profile.

The cell substance gives evidence of structure, to the extent that one sees a condensation of the cytoplasm at the periphery, which condensed plasm is designated **ectoplasm** and passes insensibly into the main mass of the **endoplasm**. The constitution of this endoplasm is a matter of debate, but it may be said to consist of (1) a reticulum, the **cytoplasm**, in the meshes of which lies (2) the **cell sap**; there are also (3) the **paraplasmic substances**. The paraplasm includes (*a*) food particles ingested, foreign or excrementitious particles that, being unassimilable, are to be cast out; (*b*) crystals or granules which have been manufactured by the cell; (*c*) the above-noted chromidial granules; (*d*) the fluid contents of vacuoles, and (*e*) inactive substances laid down as a framework in the cell, such as fibrils or calcium deposits. Altmann has pointed out the existence of fine granules which are called by his

Fig. 3

Cell bridges of "prickle cells" of epidermis. (From a photograph by Schridde.)

name, but of which the significance is as yet not understood. Lastly, at certain times specially connected with cell division, and preceding this process, a **centrosome** appears which is of cytoplasmic origin. From this centrosome run fine rays of the cytoplasm, and before nuclear division occurs it divides. As to its function, there is no agreement.

Cell Connections.—There is a definite connection between cells, although it is not an easy thing to prove; the botanists first were able to show that fine connections of protoplasm bridge the space between cell and cell, and the cog-wheel appearance of the so-called prickle cells of the epidermis is due to fine protoplasmic extensions running from one to another, while the endothelial cells that line the blood-vessels have like junctions. We can even go so far as to observe that in the eggs of sea-urchins, when the cells cleave one from another in the 8- and 16-cell stage, fine protoplasmic threads reach across the intervening space, and, in these, granules can be seen to stream from one cell to another. The detached cell is the exception, not the rule. The leukocyte, it is to be noted, is a wholly independent cell, but if we follow the leukocyte downward into the lower invertebrates, we find that the corresponding cells have series of connecting processes. The nerve cell or neurone is, according to present teaching, wholly detached, at least from other neurones. Granting this, we may say that the individual is not a colony of separate units, as blocks in a pavement, but a connected whole in which the individuals are, in general, semidetached.

The Significance of the Cell.—The cell's most noteworthy character is its minute size; few cells are large enough to be seen by the unaided eye; when they are, we find one of the following circumstances:

1. The cell may contain much stored-up food material, as in the ova of many species; the cytoplasm forms a thin skin over the food material or yolk, and in this "skin" lies the nucleus.

2. The cell may have its protoplasm developed into radiating processes, as in the infusoria; the nucleus and every part of the cell remains close to the surrounding medium.

3. There may be great enlargement of the cell associated with the development of multiple nuclei.

It will be noticed that in all these cells, large though they become, every particle of the cytoplasm is near to the surface, if not to the nucleus, and that **there is a relationship as regards size between the nucleus, the cytoplasm, and the surrounding medium** (Hertwig's nucleoplasm ratio); this relationship is determined by the size of the nucleus. The nucleus is the dominant part of the cell, governing the cytoplasm, and this governance must depend on the contact of nuclear matter and cytoplasm; so that the nucleus which has the largest surface relative to its mass, will, other things being equal, be exerting the greatest effect upon the cytoplasm, will be the most active. If the nucleus be very large it is conceivable that the centrally situated nuclear material

may be comparatively inactive, so that we may say that the little
cell, whose nuclear mass is small compared with its surface, will be
active, and fitted to survive, while the cell whose nucleus is of large
mass and small surface, relatively, will be compelled to divide, and so
increase its nuclear surface or be handicapped in the race. This is
the principle on which is developed the multinucleate cell.

If this be true of the interaction between nucleus and cytoplasm,
it holds also for the cytoplasm and the surrounding medium. The
external surface of cytoplasm can be greatly increased by prolonga-
tion into processes, but with the disadvantage that some of the cyto-
plasm is far removed from the nucleus; the most economical form is
the spherical. This indeed is the form naturally assumed by a semi-
fluid or fluid mass suspended in another fluid under the influence of
molecular interaction and surface tension. We now recognize with
increasing force that this surface tension is of basal importance in
cell activities. As the cell absorbs material and the cytoplasm
increases, the surface becomes less, relative to the increasing mass,

FIG. 4

Cell bridges of vascular endothelium.   (After Kolossow.)

and the efficiency of the cytoplasm with reference to the surrounding
medium becomes less. The cytoplasm can now increase its surface
only by division, and thus the multinucleate cell leads to the multi-
cellular organism. **The multicellular organism is thus to be regarded
not as a coöperative society brought about by the fusion of separate
individuals, but rather as the optimum amount of protoplasmic matter
of any particular order capable of economic existence as a single mass
in any particular environment,** the maximal amount and maximal activity
of such protoplasm being attained by nuclear and cell division.

THE PHYSIOLOGY OF THE CELL

The views that we state regarding the nucleus as the dominating
part of the cell are not everywhere taught at the present day. But it is
fully established that, without a nucleus, growth and reproduction of
the cell cannot occur. The cell deprived of its nucleus can be the seat

of certain metabolic activities, but the cytoplasm is progressively used up and is not renewed, there being no cytoplasmic or nuclear material formed. On the other hand, the nucleus without the cytoplasm is equally incapable of regenerating the cell, for it has been proved that there is a minimal limit to the amount of cytoplasm necessary for its combined existence. If there be less cytoplasm than this, no growth or regeneration can occur, and we add this statement to what we have already said of the dominance of the nucleus, that nucleus and cytoplasm are equally essential, though not of equal value to the cell. The nucleus cannot treat directly with the medium around the cell, but requires the intermediation of the cytoplasm for its vital processes. We need only refer to the part played by the nucleus in cell division, to the series of processes by which it insures that each daughter cell obtains its share of the nuclear material, to the part it plays in fertilization and the reproduction of the individual, and we shall refer in some detail to the great activity of the nucleus in cell metabolism. In basing its dominance upon these facts, we do not lose sight of the fact that the cytoplasm is able to manifest certain definite, if lower, vital activities, such as absorption, respiration, mobility, and contractility, and these independently of nuclear control.

FIG. 5
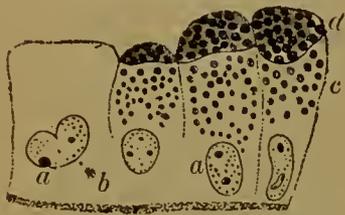
Relationship of nuclear plasmasomes to zymogen granules and secretory substances of secreting cell: *a*, intranuclear plasmasomes (nucleolar bodies); *b*, granule (extranuclear plasmasome or chromidial body) in cytoplasm, near nucleus, having same staining reaction as, and evidently discharged from, the nucleus; *c*, conversion of same into more feebly staining secretory (prezymogen) granules; *d*, further stage; zymogen granules about to be discharged. (After Maximow.)

The Part Played by the Nucleus in Metabolism.—The specific function of certain cells, especially certain secreting cells, seems to be governed largely by the nucleus. The calcareous frame of the foraminifera is not formed if the nucleus be absent; the amœba cannot fully digest, though it can kill living organisms if it have no nucleus; the formation of chitin in insect cells occurs only when the nucleus is present, and the nucleus is essential to the production of slime by the amœba. In mucous goblet cells and in the cells of salivary glands the process of secretion is accompanied by and probably depends upon the separation from the nucleus, and that more especially through the nucleolus, of granules, or **chromidia**, which stain deeply at first while they lie near the nucleus, and stain less deeply as they move away, until they appear actually to become the secretory granules. The secretory granules are either actually extruded parts of the nucleus, or the products of interaction between such extruded parts and certain constituents of the cell body. The "prezymogens" of the cell are given off from the nucleolus, and in the cytoplasm become zymogens, being again given off from the cytoplasm as specific secretions.

The formation of fat in fat cells is evidently a nuclear process, for

the vacuoles in their nuclei give the reaction for fat, and have some-
times been fixed at the moment of extrusion into the central fatty
globule of the cell. It is long since the changes were described which

Fig. 6
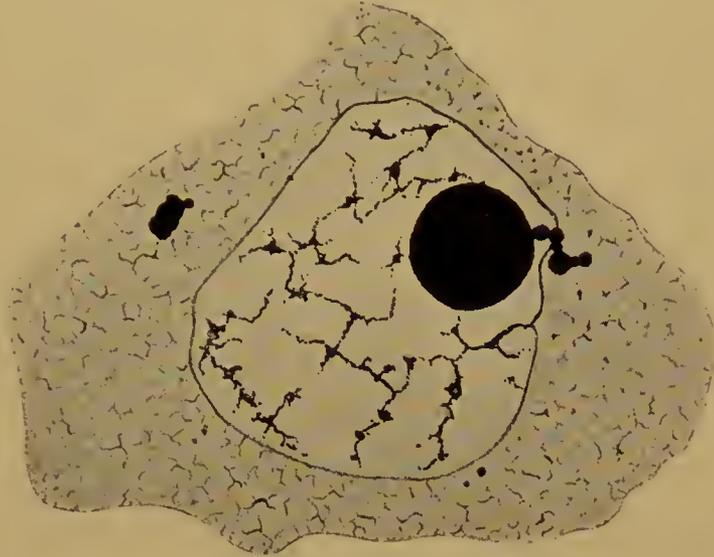
Developing egg of *Antedon bifida*, showing extrusion of nuclear matter. Young oöcyte, the nuclear
chromatin in the form of scattered branching threads. The deeply stained nucleolus is seen in the
act of extruding spherules (chromidia) into the cytoplasm. × 2000.

the nucleus undergoes in salivary cells during and after secretion, and
nuclear alterations have been frequently observed in the nerve cell
bodies of vertebrates after natural and experimentally produced fatigue.

Fig. 7
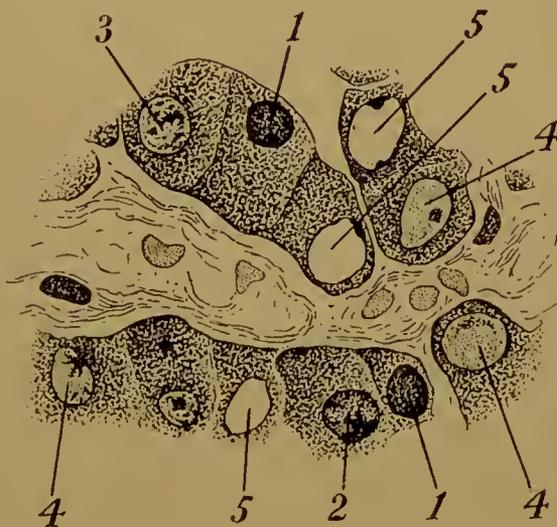
Section from the liver of a child that died from acute sepsis, to show various stages of karyolysis
of the first order: 1, unaffected nucleus; 2 and 3, paler staining nuclei, with some swelling and diminu-
tion of chromatin; 4, nuclei still more swollen, the membrane only and an occasional nucleolar mass
taking on the stain; 5, nuclei present as little more than unstained vesicles.

The changes in fatigue in the Nissl bodies, which are of nuclear origin,
are very noticeable. In general it may be said that, taking the resting
cell, under moderate stimulation its nucleus increases in size and in the

amount of contained chromatin. This increase may persist for a considerable time; if, however, the stimulation is continued for too long a period, or if again it be too severe, the chromatin becomes used up more rapidly than it is produced: the nucleus stains more feebly and either shrinks or becomes œdematous, and later vesicular, little beyond the inclosing nuclear membrane continuing to stain. Besides this **karyolysis**, or reduction of the chromatin, and œdema there may be still further grades of alteration; such are abnormal arrangement of chromatin with clumping (**karyorrhexis**), vacuolization, nuclear disintegration, with scattering of masses of the chromatin throughout the cytoplasm (**pyknosis**).

Fig. 8

Leukocytes with disintegrating masses of nuclear material scattered through the cytoplasm (karyorrhexis).

Summary.—The following summary of our conception of the physiology of the cell may be given:

i. The nucleus is the dominating part of the cell, which cannot act save in association with the cytoplasm.

ii. The nucleus initiates growth, reproduction, and often function, and reacts upon the cytoplasm, taking substances from it and yielding substances to it, but not acting directly upon the medium which surrounds the cell.

iii. The cytoplasm takes up and acts upon matter from without and gives out in turn other substances; this it does partly on its own account and partly as intermediary for the nucleus. These acts it performs in the process of absorption and respiration.

iv. It can be mobile and contractile.

Lastly, we only mention another important class of activity, the production of organic ferments by cell metabolism; these can be discharged from the cell, and can act as intermediate bodies between the external medium and the cytoplasm. The indications are that some, · at least, if not all of these enzymes are of chromidial and, therefore, nuclear origin.

THE CHEMISTRY OF THE CELL

All cells possess, in common, water, lipoids, and proteins; the proteins, at least, are to be extracted from all cells as soon as they are dead, and exist in the living cell as such, or as proteidogenous substances, which give origin to proteins. There are many other substances to be found in cells, such as salts, alcohols, carbohydrates, and so on, and many of these we regard as products of disintegration of proteins or as going to be built up into proteins. None of them, however, is common to all cells. Although proteins are dead, inert matter, and have undergone change before we obtain them, yet we believe they are bound up intimately with what we call "life," and

when we refer to the active, living part of the cell as composed of **biophoric**[1] **molecules**, we mean proteidogenous matter; that is to say, matter which, by rearrangement of its molecules or satisfaction of its affinities, becomes converted into proteins. The lipoids above mentioned are, as will be pointed out later, closely related to the proteins.

Proteins and Lipoids.—The Constitution of Proteins.—Proteins are complex compounds of nitrogen, carbon, oxygen, hydrogen, and sulphur; some, too, contain iron and phosphorus. So large and so complex are the molecules that in general they are incapable of crystallization and remain in a colloid state; some of the simplest proteins, it is true, are crystallizable, and can be obtained pure. The hemoglobins (in the plural, for they are multiple) have been analyzed, and samples from different species of animals have varied between $C_{680}H_{1098}N_{210}O_{240}FeS_2$ and $C_{712}H_{1130}N_{214}O_{245}FeS_2$; and they are among the simplest. The molecules of many proteins are far larger, and an average molecular weight for a protein has been estimated as 15,000; it can thus be understood that many protein molecules do not make their way through animal membrane, and do not diffuse.

Classification.—We speak of proteins as **free** or **combined**. Free proteins are the albumins (serum albumin of blood, egg albumin), the globulins (serum globulin, fibrinogen), and the vitellins (the "yolk plates" of egg yolk).

The **combined** proteins are in combination with various bodies, including other proteins. **Hemoglobin**, for example, can be broken up into hematin or more accurately hemochromogen—an iron-containing body with protein characters—and globin, an albuminous matter which, according to Gamgee, is not a globulin. The **nucleins** are compounds of protein and **nucleic acid**, which, in turn, is a compound of phosphoric acid and the so-called **nuclein bases**; the nuclein bases are closely related to proteins. The nucleins, again, combine with free proteins to make the **nucleoproteins**. These and yet other proteins combine with carbohydrates to make **glycoproteins**, important among which are the **mucins**.

It has been said that if individual specimens of proteins be analyzed they do not give identical proportions of C, H, N, and O. All of them, however, may be broken up into simpler bodies, which, in turn, have proteid characters. This is true not only of the **combined** but also of the **free** proteins; for example, proteolytic ferments break down albumin, globulin, myosin, etc., into **peptones**, and **albumoses (proteoses)**, which are still proteins but with smaller molecules; smaller molecules they possess, because they can diffuse through membrane; the peptones, etc., are degradation products of the proteins, and we can infer that the ordinary protein molecule is a combination of like molecules, and is thus an example of polymerization, or the formation of a large molecule by the aggregation of a series of smaller ones which are alike,

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[1] βίος, life; φέρειν, to bear.

or of like order. The peptones and albumoses afford a still further series of degradation products, the group of the **amino-acids**, which together make up about three-fourths of the albumin molecule. These amino-acids are first cousins of the fatty acids, are indeed fatty acids with qualities tending to be basic by the addition of NH_2 molecules; which again by hydration or by the addition of an OH molecule become the hydroxyl fatty acids. These amino-acids, always present as degradation products of protein, are in reality the basis of proteins; the protein is built up by a linking together of numerous amino-acid molecules.

Chemists have now been able to obtain pure, and to study, a series of these amino-acids, and have been able to obtain optically active forms of them, the significance of which fact will appear. It had been noted for a long period that if a substance were the product of vital processes, it was optically active, but if it were synthetically produced by the chemist, it was optically inactive. The optical activity of the new synthesized amino-acids indicates that they are, so far as human observation can go, absolutely identical with the amino-acids of the body.

The amino-acids are **amphoteric**, that is, they possess both acid and basic properties, acid by reason of their COOH group and basic by the NH_2 groups, and it is this duality of affinity that permits linkage. To use a homely simile, let us imagine the place of an amino-acid taken by a man, with two artificial arms; at the end of one is a hook (the basic affinity), at the end of the other, a ring (the acid affinity); if there were a large number of such men they could form a complete circle, hook in ring, hook in ring throughout the entire group. If, now, we imagine the children of each man hanging on to his coat tails, we have a large colony (the compound molecule) depending for perfect cohesion upon the hook and ring men. These rings of varying number of amino-acids are the **polypeptids**, and a linkage of eighteen individuals has been experimentally obtained. It is not even necessary that the links should be the same amino-acids, just as it is not necessary that the men be of the same race. These synthetic compounds prove by their character to be all but identical, if not identical with the peptones of the body.

The conception we have here given may be erroneous in particulars, but we have attempted to give the idea that the complete molecule is a ring, and that ring we have suggested by the bizarre simile of the group of men hand in hand or "ring in hook." This, be it remembered, indicates only the simpler molecule; the more intricate proteins, polymerized forms, are aggregations of such rings, and it will readily be seen that a very slight change in the individuality of one sub-group will change the composition of the whole. Reverting to the group of men with the children hanging on to their coat tails, we have to picture these groups as being surrounded by a concourse of individuals, who are constantly moving to and fro; such a picture, for example, as a bird's-eye view of a fair ground would afford; these individuals

(ions or radicals) as they pass a group invite (by their unsatisfied affinity) an individual of the group to leave it, and every now and then one of these free individuals is impelled to attach itself to a group. Let us suppose we have twenty such groups, and this compound group (or giant molecule) by actual count has this formula: $White_{200}$, $Negro_{250}$, $Indian_{85}$, $Chinese_{50}$. If a couple of children stray away the group becomes $white_{200}$, $negro_{249}$, $Indian_{84}$, $Chinese_{50}$, and the group is no longer the same. This is precisely what is occurring in the giant molecules of the body; the arrival of a new ion of food material, the separation of a few ions of excreted matter make for the moment a new aggregation, and these small changes mean a constant rearrangement, and constitute the metabolism of living matter.[1]

The Chemistry of the Nucleus.—The composition of the nucleus differs from that of the cytoplasm; **it contains no potassium, no carbohydrates, and, speaking generally, no fats, but, on the contrary, does contain phosphorus and "masked" iron (that is, iron in a complex ion), which appear in the cytoplasm but rarely and in small amount.**

The proteins of the nucleus show some peculiar characters; gastric juice will dissolve ordinary proteins, but the nucleus of a cell is resistant to it, because its nucleoproteins consist of albumin and nuclein combined, and the latter is resistant. **Nucleins** contain 2 to 9 per cent. of phosphorus, can be split up into albumin and a nucleinic (or nucleic) acid, of which there are several. Nucleinic acid can be further disintegrated into the **xanthin** and other **purin bases** (uric acid, xanthin, guanin, adenin, and hypoxanthin). These derivatives are important clinically because they exercise a toxic effect upon tissues, especially the kidney, and it is these which constitute the drawback to a protein diet in persons whose powers of elimination are imperfect. The existence of phosphorus and the xanthin-base groups constitutes the difference between the nucleus and other protoplasms. These groups and the "masked" iron and phosphorus are specially concerned with oxidation, the importance of which for the cell is absolute.

Before leaving this part of the subject we would recapitulate our idea that the "biophoric molecules" or masses are the active part of the cell; that they are huge molecules aggregated of many large groups, of which each may be considered a ring of molecules with affinities which are being satisfied by various other groups; that some affinities are constantly unsatisfied; that ions and molecules are being shed off and taken on, and groups are joining groups by new affinities, that groups are breaking off and that this activity means metabolism, means **life.** It must be understood, too, that while from moment to moment the composition of the biophore may vary, the average composition over long periods of time remains the same.

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[1] For a fuller statement of these views regarding the structure of the protein molecules see Adami's Principles of Pathology. A very clear expression of similar views is given in the first chapter of Vaughan on Protein Split Products (New York and Philadelphia, 1913), a work that well deserves study.

Enzyme Action.—We lay stress upon a proper understanding of enzyme action because we regard it as being a type of much of what we call metabolic processes in the cell; we shall constantly recur to the conception here indicated. We understand first of all, that there are enzymes[1] in the cell and enzymes outside the cell, the latter being elaborated in the cell and discharged. Each enzyme acts upon a particular substance or series of substances in the external medium— ptyalin upon starches, making sugars; pepsin upon proteins in an acid medium, making peptones; trypsin upon proteins in an alkaline medium, and steapsin upon fats. It is not possible to obtain the enzymes free from combination with protein bodies; as the proteid material disappears from the solution the enzyme action disappears. Finally, an extremely minute amount of combined enzyme and protein can convert a maximum amount of fermentescible substance, and yet the enzyme itself be not used up; the action does cease, however, when the products of fermentation have accumulated up to a certain point.

It will seem strange to the reader, at this juncture, to say that enzymes do not exist, but such seems to be the case. Enzyme action does, but enzymes as definite chemical entities in all probability do not. Enzyme action is an interaction between a proteidogenous molecule, and a fermentescible substance present in the same medium, part or the whole of the molecule acting on part or the whole of a molecule of the fermentescible substance with the result that a new substance appears—the product of fermentation.

The Enzymes.—Enzymes are **intracellular** and **extracellular**; the former act in such close combination with the biophore, the compound protoplasmic molecule, that we have to conclude that their action is part and parcel of the activity of the biophore. This is proved by the fact that such enzymes cannot be extracted, in fact, are not existent in the molecule unless it be alive. If this be true of the intracellular enzymes, it is also true of the extracellular; these enzymes, in fact, are free protein molecules, divorced from cellular relationship, but still manifesting a characteristic of life, viz., that of being able to act upon other molecules and cause their rearrangement.

Some hold that enzymes act by **katalysis**, but this view we do not advocate. They consider the ferment as a body possessing active molecular vibration, so that, in apposition to molecules of the fermentescible substance, it communicates to them its vibration, with the result that their particles are shaken into a new arrangement and the fermentescible becomes the fermented substance. This is the explanation given of the process by which finely divided platinum converts hydrogen peroxide into water and oxygen, and this process is katalysis. A more satisfactory explanation of ferment action seems to be that exemplified by making sulphuric acid from sulphurous anhydride by the mediation

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[1] To prevent confusion we employ the term *enzyme* to designate those ferments which are produced by the living cell, to distinguish them from inorganic ferments, *e. g.*, gold and platinum.

of nitric acid; the nitric acid gives up an atom of oxygen which converts the sulphurous anhydride to sulphuric acid, thus:

$$H_2SO_3 + HNO_3 = H_2SO_4 + HNO_2$$

The nitrous acid, so formed, exposed to the air, combines with its oxygen and forms nitric acid, thus:

$$HNO_2 + O = HNO_3$$

Theoretically, a single molecule of nitric acid can convert an infinite number of molecules of sulphurous anhydride into sulphuric acid and at the completion of the action (if infinity could be completed) still exist as a molecule of nitric acid.

FIG. 9
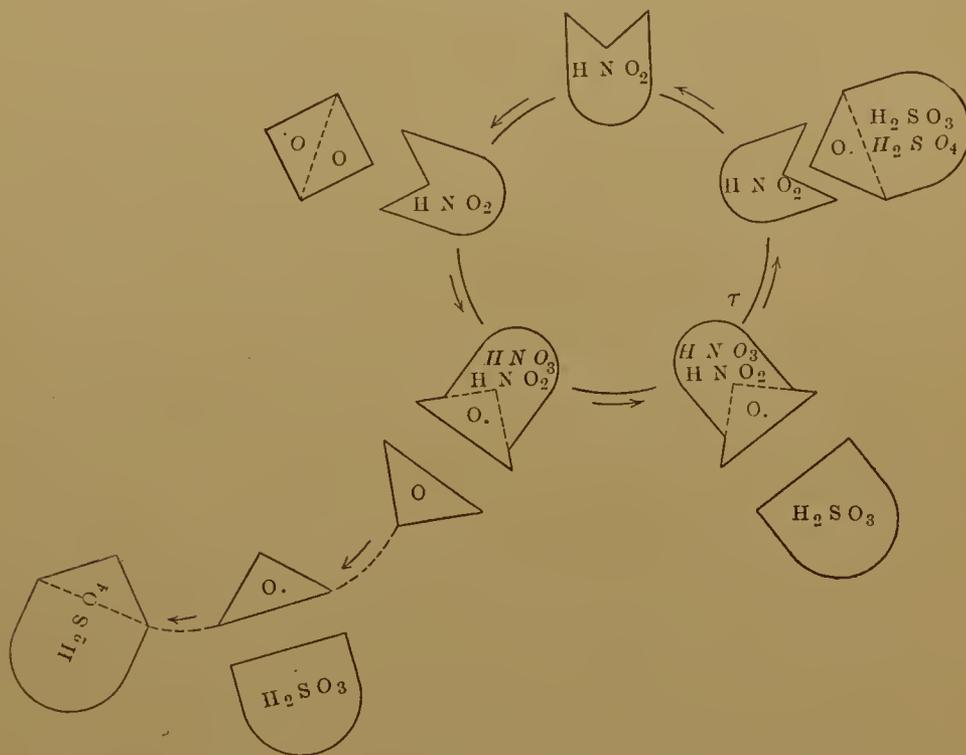
Schema of ferment-like action of nitrous oxide in the formation of sulphuric acid from sulphurous anhydride. The completed circle represents the successive stages of activity of the HNO_2 molecule, first attaching to itself an O molecule from an O_2 combination, and then yielding this to an unsatisfied H_2SO_3 molecule. To the left of the diagram it is suggested that the other O molecule liberated from the O_2 combination may also combine with an H_2SO_3 molecule to form a second molecule of sulphuric acid.

In this process there are three factors—the sulphurous anhydride represents the fermentescible substance, the oxygen the fermentator or complement, and the nitric acid, which alone is present in both reactions, the ferment. The process can be represented as above.

If instead of the bodies in the above picture, we consider that we are dealing with protein molecules with their unsatisfied affinities, we can conceive the process as being instigated by their unsatisfaction and concluded by their satisfaction. Enzyme action is one form of the interactivity of the biophores. This being so, one of our com-

pound protein molecules may be intermediary body, or it may be fermentescible substance; or, since each individual part of the huge ring has its own peculiar characters, and its own unsatisfied affinities, the same huge molecule may be in a sense both at the same time. If we consider the biophore in activity, reacting thus, let us say, with proteins in the food and discharging fewer metabolites than it attracts, we find it getting gradually larger. This is **growth**.

At this point we may review the subject, pointing out that we have now three orders of proteidogenous matter concerned in metabolism: (1) **Nuclear matter**, capable of metabolism and growth in a medium of proteins; (2) **cytoplasmic matter**, capable of independent metabolism, but incapable of growth save in combination with nuclear matter, and (3) **the free organic enzymes**, capable of causing metabolism, but incapable of growth. Are we to admit all these into our conception of what is living matter? This is a moot point. For ourselves, we are inclined to regard growth as the all-important property of living matter; but if this view be accepted, then it may be held that the biophores situated within the nucleus are the only truly living elements within the cell. This is contrary to the usual conception of the cytoplasm as being also living matter; the question must be left open.

The Reversibility of Enzyme Action.—Since we count enzyme action so important for an understanding of metabolism, we must indicate that it is reversible, and in fear of making the subject too complex, we shall merely exemplify this. The enzyme **maltase** splits up maltose ($C_{12}H_{22}O_{11}$) into two molecules of glucose ($C_6H_{12}O_6$), but in the test tube the reaction is never complete—there remains a mixture of maltose and glucose. Maltase really can split up maltose into glucose or build up glucose into maltose, and so long as the products of disintegration or of synthesis remain in the solution, neither the glucose nor the maltose can be used up. The enzyme will cease to act *when a stage of equilibrium is reached*, when the tendency to disintegrate the one balances the tendency to synthesize the other. This action may be expressed thus:

$$C_{12}H_{22}O_{11} + H_2O + Maltase \rightleftarrows C_6H_{12}O_6 + C_6H_{12}O_6 + Maltase.$$
$$\text{Maltose.} \qquad\qquad\qquad \text{Glucose.} \qquad \text{Glucose.}$$
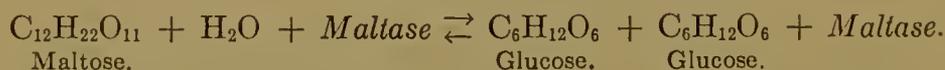
We have at the present writing evidence to indicate that all enzyme action is potentially reversible (although recently it has been shown that the reversed action may require a temperature different from that required for the original action), and this of itself is good evidence in favor of the supposition that an enzyme is not a chemical entity, but *a varying state of satisfaction between the affinities of two molecules.* What was meant in saying that the enzyme as an entity does not exist may now be better understood. Equilibrium and arrest of enzyme action occurs when the products of that action accumulate up to a certain point, while, if the products be removed, it goes on until all the fermentescible substance is used up. In the alimentary canal, the

products of action of the various extracellular enzymes are absorbed, finally reaching the lymph; in health, thus, the proteins, starches, fats, and other food substances become fully disintegrated. In the cells, the action of the intracellular enzymes occurs, and its extent is largely a matter of diffusion. Take, for example, the glycogenic activity of the liver cell. For our purposes we can regard that cell as a sac, suspended in the lymphatic fluid, formed of a lining membrane which permits certain substances to diffuse freely in one or other direction. Among other contents are **glucose** and **glycogen**. If the cell in its metabolism has burnt up the glucose it has, and becomes deficient in carbohydrates, more glucose will diffuse in; the ferment in the cell will synthesize this to glycogen, and will continue so to do till there is a local equilibrium between the intracellular glycogen and sugar (glucose). Glycogen, being insoluble, remains in the cell, stored up. There it remains until one of two things happens: until either (1) the cell is using up glucose faster than glucose can diffuse into the cell from the lymph, and the glycogen-glucose equilibrium is destroyed, when the reverse enzyme action begins to break down glycogen till so much glucose is formed that the equilibrium is restored, or until (2) the glucose in the lymph is reduced to a point below the amount in the cell by the tissues using it up faster than the alimentary tract supplies it. If this happens, the glucose, being soluble, diffuses out into the lymph, and similarly the glycogen-glucose equilibrium is destroyed; the ferment action will break down glycogen again, and if the equilibrium be not restored by a fresh supply of glucose, the glycogen of the cell will be used up.

This process we have just described, **essentially an enzyme process, is really what we have been accustomed to call metabolism;** the cell equilibrium depends upon the enzymes in the cell quite as much as, or more than upon the material absorbed. If the enzymes of the cell be interfered with, the essential agent in absorption is lacking, and we find disturbance of metabolism. As free enzymes in the cell are associated with discharge from the biophoric molecules forming the nucleus, we see how the foreign agents of disease, by disturbing the biophores, strike at the very foundation of metabolism, nutrition, and the well-being of the body.

Lipoids.—During the last few years, the importance of the lipoids in cell activity has been more and more recognized. Under this term we include those bodies which have the common property of being dissolved, like ordinary fats, in ether, alcohol, chloroform, etc. Nearly all of the bodies having this property are fatty compounds, hence the term lipoid, although it is usual to include here also cholesterin, which has no fatty moiety. They may be classified as:

I. Bodies containing neither phosphorus nor nitrogen: fatty acids, neutral fats, soaps, cholesterins.

II. Nitrogen- and phosphorus-containing lipoids. The **phosphatides,** such as lecithin (a glycerin phosphoric-acid ester of two fatty acids plus cholin) and kephalin (having two fatty acids and two bases),

as well as sphingomyelin, the most important constituent of the so-called protagon of brain substance.

III. Nitrogen-containing phosphorus-free bodies, *e. g.*, the **cerebrosides**, which resemble glucosides in their composition.

IV. Bodies of fatty nature, not yet analyzed, *e. g.*, the lipochromes.

Recent investigation indicates that the lecithins and cholesterins are intimately associated with the development of protective substances of the body and the production of immunity.

Fats, Soaps, and Alcohols.—This group of metabolites may possibly be split off from the cell protein; they are not found in the nuclei (save, as already noted, that fat has been found in nuclear vacuoles), and are to be considered as acted upon mainly by the cytoplasm. Certain cells are found to contain insoluble neutral fats of which the most important are **stearin, palmitin**, and **olein**; these fats, according to their formula, contain a very small quantity of oxygen with a relatively large amount of carbon, which means that their dissociation and combination with absorbed oxygen is capable of setting free a great amount of energy; hence their value to the cell.

These come from the food almost entirely as neutral fats; they are emulsified by the action of the bile, and, to some extent when emulsified, may be absorbed by the phagocytic action of the intestinal epithelium and leukocytes. But this is by no means all. It would seem that free fatty acids are to some extent split off, soaps being formed and glycerin liberated; while again there may be actual solution of the fats by the colloids of the cells and body fluids. This matter is not yet determined. The presence of the fat-splitting ferment **steapsin** (discharged by the pancreas) in the intestinal contents favors the division of the fats into free fatty acid and glycerin. The latter is probably taken up by the intestinal epithelium; the fatty acids are partly dissolved by the bile salts, but most of them, in an alkaline medium, are transformed into **soaps** of sodium, potassium, calcium, and magnesium. As soaps they pass through the intestinal cells and are to be found in the chyle and lymph as neutral fats. Neutral fats are rarely found in the blood, while soaps commonly are; so it is evident that a second conversion occurs; it is as soaps that the fats are ultimately taken up by the cells.

Microscopically, the cells of an organ, *e. g.*, the kidney, may show no fat nor do they yield fat forthwith to ordinary fat solvents; yet the dry substance of such a kidney affords as much as 17 per cent. of fat; this means that the fats here are not free, but combined.

Soaps are evidently very important as an intermediate stage in the utilization and synthesis of fats; lipolytic and fat-forming ferments have been isolated and designated **lipases.**

Do proteins give origin to fats or fatty acids? They probably do to a slight extent, but at present it appears as if the fats of the body are almost entirely the fats of the food.

The **lecithins (phosphatides)** are almost constant constituents of

the animal cell, and form a considerable factor in nerve cells and in the cells of egg yolk. They have a fatty portion indicating a relationship with the proteins; and they are richly phosphorized. The last two facts suggest that they are cleavage products of the nucleins, or combinations of such cleavage products with fats.

Parallel to the lecithins as protein-fat compounds are the **glycoproteins** —or protein-carbohydrate compounds—chief of which are the mucins. These are to be seen in the cell as globules of mucinogen, which by imbibition of water become mucins. They are modified, largely inert, proteins; among them are gelatin, elastin, chondrin, amyloid, and mucin, which are poor in carbon and rich in oxygen, and yield on dissociation carbohydrates. A few other "albuminoid" materials occurring in and outside the cell are to be mentioned: the products of dissociation of hemoglobin, such as hematin, together with melanin, the pigment of the skin and hair, which recent observations indicate are allied to the lipochromes, compounds of lipoids with protein derivatives. These will be discussed with the infiltrations and degenerations.

Water.—Cell activity is associated with the presence of water, water being the medium in which metabolism occurs. If the amount of water be reduced below a certain percentage, latency of activity supervenes, and if the water be removed entirely, molecular death; 60 per cent. of the human body is water, and 80 per cent. of certain organs, such as the kidneys. The average cell of the human body may be considered as seven-tenths water and three-tenths proteins and other constituents. It is still debated whether living matter is existing in a soluble state in water, or as solid undissolved molecules suspended in a fluid medium. As to whether the cell is liquid or solid, it may be said that the relation of molecule to molecule is variable, and yet at times is relatively fixed; the truth is that **protoplasm is colloidal**, that is, the molecules are so large that they cannot enter perfectly into solution, and as a colloid it possesses many of the properties of a liquid together with the persistence of form characteristic of a solid body. Our idea of a solution is that the molecules of the dissolved body lie in the interstices of the solvent: in a colloid, protoplasm for instance, we have to imagine the molecules of water as lying in the interstices of the huge protein molecules. The question is of importance because of what we know of **ionization**. When NaCl, for instance, is dissolved in water some of the molecules become dissociated into Na and Cl and these free constituents are charged, some with positive electricity (**anions**) and some with negative (**kathions**); these act as separate molecules, and may be attracted by molecules or by other ions having an opposite charge. By increasing the dilution all the molecules may be thus ionized. Stable chemical compounds are made by the union of such ions—or electrolytes—with liberation of energy. Such compounds may be broken up by *heat* or *electricity*, on the one hand, or, on the other, by *solution*, and the dissociated ions are ready for fresh chemical combinations; the assimilation of food by the cell depends

3

upon the separation and rearrangement of ions. If this is not to be accomplished by heat it must be done by solution, and water becomes an essential. **It seems thus that the relatively abundant water of the cell offers a means whereby chemical changes—metabolism—may be carried on with the least expenditure of energy and greatest economy.** Enzyme action is largely accomplished by **hydrolysis**, and the setting free of active hydrogen and hydroxyl ions in a watery solution, and these ions are most important in the process of metabolism.

Simple Salts.—Certain salts without being built up into the protein molecule are obviously essential to the cell, for the protein molecule does not exert its activity in a pure watery medium, but in dilute saline solution. The salts usually met are chlorine salts, alkaline carbonates, phosphates, and sulphates, and salts of the alkaline earths, especially sodium, potassium, ammonium, calcium, and magnesium. We know little about their disposal, but we assume, from the minute quantities present, that they probably are mostly dissociated into their ions and so help to promote activity of metabolism. The dissociation of salts, and their building-up into the biophore are accompanied by various phenomena which we call **endosmosis** and **exosmosis**, which is the diffusing, into or out of the cell, of water and salts in solution. A salt of high concentration in the cell will pass out of the cell to a medium where the concentration is lower, and *vice versa*, and at the same time a corrective reverse passage of water occurs. The colloidal cell substance is sufficiently permeable to allow the molecules of the salt in solution to pass. We believe, too, that colloids of different composition differ in their permeability, and, therefore, in the time required for the passage through them of solutions. This relative impermeability of the colloidal skin (**ectosarc**) of the cell explains why the huge protein molecules are kept in the cell while the smaller, partly dissociated ones can escape. There are some of these which are almost small enough to escape, and their retention depends on the state of the cell in relation to the external medium, depends upon the nature of the cell membrane and upon its surface tension. An example of this is found in the red corpuscles, which lose their hemoglobin when the salt in a salt solution reaches 0.47 per cent. If the osmotic pressure be less than this, salts diffuse out and water in, till the ectosarc is ruptured and the hemoglobin is dissolved in the surrounding medium and colors it. But corpuscles do not lose their hemoglobin till the osmotic pressure is much higher than the tonicity of the serum of man (0.9 per cent. sodium chloride). Solutions with an osmotic pressure higher than this are **hyperisotonic**, with one lower, **hypisotonic**. The blood serum must be very hypisotonic before hemoglobinemia, from passage of the hemoglobin out of the cells, can occur purely from this cause.

Carbohydrates.—Free carbohydrates as such do not enter into the composition of the biophore, and when found in the cell are true **metabolites**; they have been or are ready to be dissociated. It must, how-

ever, be recalled that the dissociation of nucleic acid yields a pentose (sugar) according to Levene and Jacobs, a hexose according to Stendel and Halliburton. From the dissociation of sugars energy is liberated, and on the contrary energy is conserved when they are stored as built-up glycogen molecules.

GROWTH

In all our previous considerations of the biophore we have dealt with metabolic activity, but we have made only passing reference to growth. If we think a little it will be seen that **the growth of living matter demands a process whereby two molecules exist where there was one before.** Our conception of the biophore is as a ring, or a ring of rings, and growth occurs by increase first of the individual smaller groups or rings. These groups, from their very inception present a series of unsatisfied affinities, and each or any of the molecules is constantly attracting molecules of a like order, and on the first of these is built up a second and a third until the group is complete. Along these lines we can imagine the development of a new ring of which each individual component is the reflection of the components of the original ring: in its turn this ring attracts, and so builds up other rings in due order until eventually there is produced a completed compound molecule, reproducing the parent molecule. We use the illustration of the ring to indicate a degree of completeness; the ring can break, it is true, and in its repair, be enlarged or be made smaller, or it can join with another broken one, but the molecules of the formed ring are less likely to be attracted away just because they are in a ring, *i. e.*, in a state of relative completeness.

The Relation between Growth and Other Cell Activities.—The consideration of this subject demands a few words on the dynamics of the cell. In the performance of function of whatever kind, the cell is a machine discharging potential energy. The body warmth means that cells are liberating energy in the form of heat; the nerve cell liberates energy akin to electricity. On the other hand, growth and the accumulation of new molecules demand, not the evolution, but the *storage of energy*, and this comes from the food. The proteins, carbohydrates, and fats are carbon-containing bodies the ultimate result of whose decomposition is a yielding of much energy. The excreta of the organism, carbonic acid, water, urea, etc., on the other hand, store up comparatively little, and the cells acquire most of the difference.

Strictly speaking, **energy is** *not* **evolved in the dissociation of matter;** but dissociation and the freeing of ions mean that combinations immediately occur which liberate far more energy than was lost in the dissociations of a moment before, so that the ultimate result of dissociation is, paradoxically, the production of energy. To give a familiar example: heat has to be applied in the first place to the wick of the

candle to light it; in other words, energy is used up in bringing the contained waxes or fats to the dissociation point; when this point is reached the resultant products combine with the oxygen of the air and in so doing evolve so much heat that flame results. **It is a similar combination of the cell substances with oxygen that is the main source of heat in the body.** The biophores are not to be compared to simple salts, but rather to nitroglycerin. A blow dissociates it, and though there is a theoretical momentary loss of energy, there is a vastly greater immediate production of energy—an explosion—brought about by the reconstruction of the ions of C, N, H with O, into more stable compounds. Dissociation, then, tends, ultimately to the liberation of energy, and growth, or building up, to the using and storing of energy, the conversion of kinetic into potential energy. The energy of the food is thus:

(*a*) **Katabiotic**, dissipated in the performance of function.

(*b*) **Bioplastic**, stored up in the formation of the complex biophore, *i. e.*, in growth.

Can these two contrasted processes, growth, and the performance of function proceed simultaneously in the cell? They can, as we shall show.

To digress again, growth is an intracellular affair, governed by conditions in the biophore, while the performance of function is a response to external stimuli of some kind. If the cell has abundant food, and the stimuli to function be strong, all the acquired energy may be used up at once, and no growth ensue. If the stimuli be yet stronger, all the food energy may be used up, and the cell substance be dissociated to supply the further energy required. If the food energy be little, the cell may require to use up its substance to provide the energy needed for function. There is, however, a grade of adequate food supply and of moderate external stimulus, in which the dissociation of the food-stuffs provides more energy than the cell is called on to dissipate and the surplus is used in growth. The development of muscles under proper exercise illustrates this. Conversely, with adequate food, and not enough activity, muscles do not develop, but the contrary; a certain optimum of activity is necessary for the maintenance of nutrition and of growth. There are apparent exceptions to this, in the embryo, in tumor growth, and in the fact that under exercise and adequate nutrition there is a limit beyond which growth cannot go. Whereas growth and function have thus a definite relationship, there are circumstances under which growth is quite independent of function.

Active assimilation and growth with little functional activity characterize the embryonic and fetal stages of existence. The more the cells become differentiated (for their proper function in different organs), the less capacity they show for growth and the more for katabiotic activity.

Growth of the cell and of the individual progresses until the volume of the cell (and of the individual) reaches the point beyond which increase

in mass is not only uneconomical, but harmful. Not only is there, as Hertwig has pointed out, a definite ratio between nuclear mass and cell mass for each order of cell, but similarly for each order of cell then there is a relation between surface area and mass, and when the mass exceeds a certain amount, the surface area is too small, and assimilation and discharge are hindered. The cell has now the alternatives of cell division (by which there is a rapid increase of surface area relative to mass) or of lessening its mass by the performance of function, that is, of dissociating some of its cell substance. As long as the cell or the individual is below the economical ratio between its mass and its surface area (relative to its external medium), it chooses the first (cell division); as this ratio is approached it tends to employ the second (functional activity.)

The size of the individual is thus a function of the constitution of the biophores; it is the expression of the optimum economy of interaction between the biophores and the external medium. We explain the apparent exceptions above noted by realizing that growth of cells and of individual continues till this optimum is reached. In the developed cell there must be a constant alternation between growth and functional activity; in performing function the cell dissociates some of its substance, and falls below the state of optimum efficiency, and it is in a position to take up new matter and grow; Weigert's statement is "the katabiotic use of material in function removes the obstruction to growth."

Physiological Inertia and Habit.—A wheel set spinning continues to spin after the hand is withdrawn; a gland stimulated to secrete continues to secrete after the stimulus is removed. A resting muscle continues to rest (during the *latent period*) before it acts in response to a stimulus. The cell, like matter in general, tends to continue in the state in which it is, whether of rest or activity. This **inertia** is the precursor of **habit**. A cell stimulated to perform an act continues to perform it after the stimulus is removed; on a second occasion, a slighter stimulus suffices to make it repeat the act, until a period is reached when a minimum stimulus will produce an optimum reaction, and the cell, tending to employ its energy in one particular direction, tends to lessen its activities in other directions. It becomes **adapted** to its work. Once a cell starts to grow it has a tendency to continue to grow rather than to perform function, until its increased size and increasing tension and other external stimuli attain such power that it is compelled to functionate. This, in turn, once started, is apt to continue. We have thus attempted to show the biological process by which one cell becomes many cells, and the many cells attain a certain size by individual growth, and finally, by which the energy that is put into growth becomes, at the proper time, directed toward the performance of function and a continuance of the same.

RESERVE FORCE

An important character of living matter is what is termed **reserve force**; upon it depends the process of healing. Just as a wall, a bridge, or a boiler, built on sound mechanical principles, is able to stand a strain several times greater than it is ordinarily expected to carry (the "factors of safety" of the engineer), so are the cells of the organism. **There is a large reserve of force or energy in them above that which they exert under normal conditions.** Illustrations of this are known to everyone. The patient who seems so weak that he can scarcely raise his arm may become in delirium a match for two men. The heart can do thrice its normal work without overstrain; three-quarters of the rabbit's liver may be removed, and the remaining quarter serve its purpose; the whole of the spleen of a dog may be excised without injury to the animal's health.

In the last case, other related tissues take up the functions of the spleen, exercising a **vicarious** activity; yet vicarious activity is a pure example of reserve force. Such also is **compensatory** activity, *e. g.*, one lung will suffice for respiration, one kidney for urinary excretion; even in the brain, one of a pair of centres can take up the work of its destroyed fellow. In short, the **organism is so constructed as to possess in most of its functions an abundant margin of reserve force.** This reserve force lies at the root of the healing of injuries and of immunity to disease.

Reserve force is yet one more result of physiological inertia. Life has been defined as the continuous adjustment of internal conditions to external changes of environment. It is more, **it is overadjustment;** when the cell assimilates, it continues to assimilate more than is needed at the moment; when it starts to grow it continues to grow above the extent of the original stimulus; and the excess remains as reserve force.

THE STATES OF CELL ACTIVITY

The state of the cell at any given moment depends upon the sum total of assimilation, growth, and external stimulus, and this state is variable, and the variations carried far in one or another direction, constitute cell disease.

1. **Subnormal Activity.**—Even in normal tissue the accumulation of reserve force leads to the presence of redundant cells, which, receiving relatively little stimulation pass into an inert, latent state. These cells, with lack of stimulation, atrophy, and some of them actually disappear. Not only does this occur with redundant cells, but even with normal cells under abnormal conditions; this can be well seen in the atrophy which an immobilized leg undergoes; and the actual disappearance of cells is seen in the cases in which the lower motor neurones atrophy and disappear as a result of lack of stimulation from the upper ones, in cases where the upper ones are destroyed.

2. **Vegetative Activity.**—Cells in the process of active growth present certain well-marked characters. The nuclei are large, round or oval, staining deeply; paraplasmic granules are not prominent; the cell body is round or oval. Cells of this character are prone to reproductive activity and have been called **embryonic** cells. The name is not a good one, because such cells occur at all life periods, and a better term for them is **vegetative** cells.

3. **Functional Activity.**—Cells in functional activity show signs of differentiation according to their specific function; in muscle or nerve cells the cytoplasm is highly elaborated; in gland cells, there are paraplasmic deposits, in the form of granules or globules; the nuclei are not large, and their staining differs according to the stage of cell activity.

4. **Hyperactivity within the Limits of the Reserve Force of the Cell.**—When increased stimulation is accompanied by adequate nutrition, the functional activity of the cell is, to a certain extent, accompanied by growth, and this constitutes **hypertrophy.**

5. **Excessive Functional Activity.**—When the cell work is extreme, the energy used up exceeds the supply from the food, the paraplasmic material disappears, the protoplasm is dissociated, and if the stimulus be continued the cell is exhausted; the nucleus stains poorly; the cytoplasm in the case of cells like those of the kidney tubules may be disintegrated and partly discharged; or there may be abnormal deposits in the meshes of the cytoplasm; or the cytoplasm may become œdematous and vacuolated.

CELL MULTIPLICATION

Increase in size of the individual is brought about in two ways: by enlargement of the individual cells, and by intercalation of new cells. We speak of increase in size of the individual as growth, whether it arise from one or the other of these processes, but it is necessary to remember that cell multiplication and cell growth are not synonymous terms. Cell multiplication is of two main types—direct, or **amitotic** and indirect, **mitotic** or **karyokinetic.**

Direct Division; Amitosis.—This is the rarer form of the two, and may be said to occur not at all in the *development* of the mammalian *body*, but in fully developed adult tissues it does occur, and is particularly frequent in cells that are multinucleate. In leukocytes and endothelial cells it occurs, and is the rule in the syncytium of the mammalian embryo, and in the rapidly growing envelopes of the embryo. In the last named, it will be noted that the tissue is but a temporary one. There seems to be a certain amount of truth in the statement that cells which exhibit amitosis are on the way to degeneration. As far as the leukocytes are concerned, in lymph nodes where cells are being continually produced mitosis is seen, and it is only in the blood

and in leukocytes in inflammatory areas that we encounter amitosis. Possibly we cannot enunciate this view so confidently as we were accustomed to do; of late years attention has been called with increasing frequency to the occurrence of amitosis in active tissues. We must, however, admit that we cannot follow the fate of cells originating by this method.

In amitosis, the nucleus divides without any preliminary rearrangement of its structure. It becomes elongated, then dumb-bell shaped, the neck breaks, and the daughter cells separate, either followed or not followed by a corresponding division of the cytoplasm. The centrosome plays no noticeable role in this form of cell multiplication.

Fig. 10

A   B
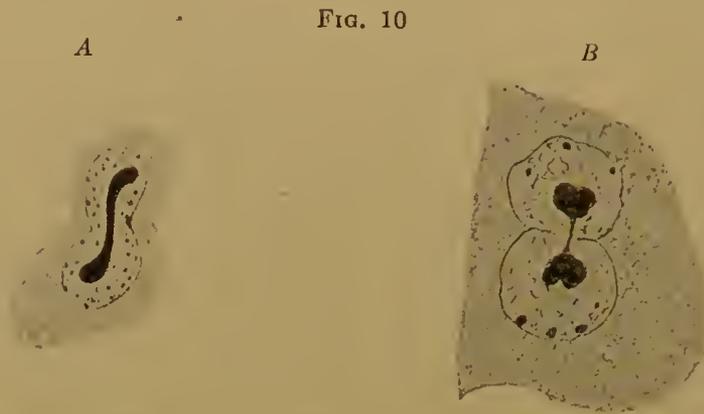
Amitosis. Stages of direct division in tumor cells: *A*, from an ovarian cancer: *B*, from an epithelioma of the lip. (Nedjelski.)

Indirect Division; Mitosis. — In this form of division the nuclear material is divided with exactness between the two daughter cells. If the nuclear material were uniform, it would not be necessary to have the elaborate "quadrille," but each daughter cell would take its half as happens in indirect division; that the nuclear material arranges itself indicates that there is a differentiation of the biophores, so that each daughter cell obtains a group of biophores identical with that obtained by the other. We shall merely indicate the stages in the process.

1. **Prophase or Preparatory Stage.**—The nuclear chromatin in the resting stage of the cell is an irregular or nodulated network; it becomes a continuous single thread which appears as if in a tangle, and then divides into a definite number (in man, thirty-two) of short lengths called **chromosomes**. As this is progressing the nuclear membrane disappears and the chromosomes lie naked in the cell. While this goes on in the nucleus changes appear in the cytoplasm. The **centrosome** appears and divides into two halves, around each the cytoplasm becomes concentrated into radiating fibrils, forming a star or **aster**, and as the two halves of the centrosome separate and journey to opposite ends of the cell, a **spindle** of fine fibrils is seen to stretch between them.

2. **Metaphase.**—Each chromosome splits longitudinally into two like halves, the daughter chromosome appearing to become attached to

PLATE I
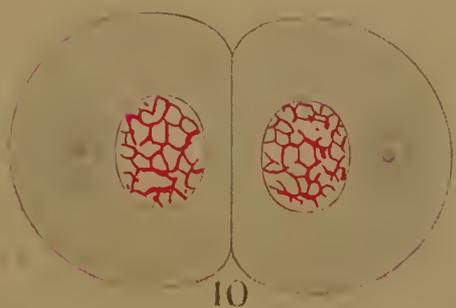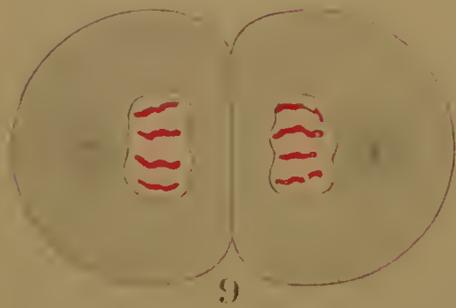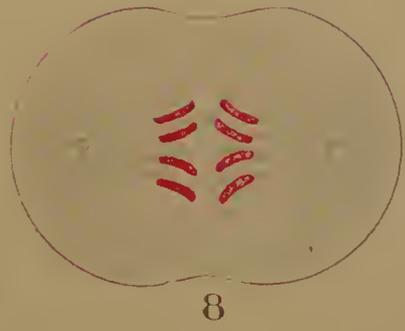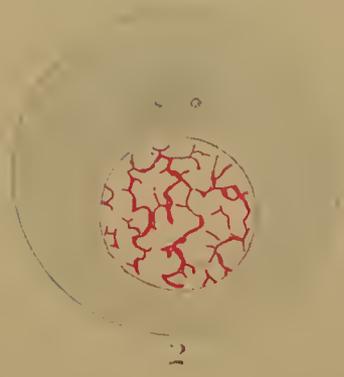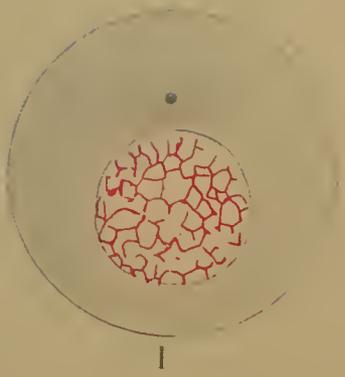
The Phases of Mitosis.

the **mantle fibres** of the spindle. This splitting of the chromosomes is the fundamental process in cell division.

3. **Anaphase.**—The daughter chromosomes diverge, a member of each pair going to one or the other pole of the spindle. Here the chromosomes crowd near the centre of the aster.

4. **Telophase.**[1]—The cell body divides into two, the line of division passing through the equator of the spindle. Each daughter cell now contains half the chromosomes, half the spindle, and one centrosome and aster. The two last may persist, as the **attraction sphere,** or may disappear. The daughter chromosomes fuse into a tangle, which becomes irregularly swollen or nodulated and forms the network of the resting nucleus.

ADAPTATION

We have already made the statement that the organism can adapt itself to its surroundings, and the doctrine of the survival of the fittest indicates that where there are many individuals undergoing change to become better suited to their environment, the ones who best meet the new requirements are the ones who survive and their progeny, so modified, force out of existence the fewer, weak progeny of those less well adapted. A large element of chance enters into such a process. This, however, while true, is not the whole truth. Adaptation is not a passive fortuitous modification of living matter in a favorable direction, but an active process, whereby a change in surroundings brings about a change in the composition of the living matter.

Examples of adaptation are numerous; bacteria which ordinarily split up carbohydrates can be made, by growing in special media, to split up proteins; bacteria which can ferment one sugar but not a second may be "trained" till they ferment the second and not the first; bacteria which were not pathogenic can be made to become so. These altered powers are due to the acquirement of new qualities by the bacteria adapting themselves to their particular surroundings; the alteration can occur in so short a time as to make it certain that it is an active process. The acquired immunity in man against disease is an example of adaptation, the cells adapting themselves to one more foreign agent, in this instance the toxins or dissociation products of the special bacterium. This adaptation may remain for a long time after the toxins have ceased to be present, because there is impressed on the cell some alteration in constitution which is passed on even to the progeny of the cell. The capacity to adapt itself is inherent in the molecules of the cell, and the molecules become changed in response to some agent or agency in the environment; it is not that the tendency to vary is inherent, but rather that the power to change in a particular direction is present, the change being in response to the action of a specific

---

[1] πρό, before; μετά, in the middle of; ἀνά, backward; τηλοῦ, afar.

agent. Expressed more concretely, a particular modification in the environment is able to change the protoplasmic molecule in a particular way. If the cell remain in the same environment with the same kinds of food molecules coming to it, the cell response will be to build up the same side-chains within limits; in short, the cell will not vary. But as soon as a new foodstuff is brought to it, and dissociated, an entirely new set of ions may be produced, and new combinations entered into, new side-chains may be built up, and the protein molecules in the cell itself thereby altered. This particular cell has gained a new character by adaptation, by undergoing a molecular rearrangement; growth goes on at the same time, and the new side-chains may be detached into the surrounding medium or may remain and be built up into the cytoplasmic or nuclear molecules. If then a cell has adapted itself, and has multiplied, the process of adaptation is not over, for its progeny will partake in the altered composition of the molecules in the parent cell.

Adaptations such as these will occur in response not only to the foodstuffs, but likewise to toxins; and changes in temperature, vibration, light, and other physical agents, not introducing any new ions or molecules may yet cause a rearrangement of the molecules in the biophore, and so an actually altered composition of the cell, with altered characters.

CELL DIFFERENTIATION

A corollary to this is that a cell becomes adapted to its particular set of circumstances, its food, and so on, and thus becomes different from its neighbor; this is the reason that underlies cell differentiation. If we begin with a cell, which multiplies itself into a mass of cells, it is obvious that the cells on the outside of the group are in a relation to the surrounding medium which differs from the relationship of those on the inside. If we begin with two separate cells, exactly similar, each of which grows into a multicellular organism, if each be exposed to exactly the same environment the daughter cells will be differentiated in exactly the same way. But if the biophoric composition of these two cells is different, even if the environment be the same, we shall have the daughter cells in the multicellular organism differentiated according to a plan that differs from the differentiation of the last example. To state this otherwise, we would say that cell differentiation is due to two factors, biophoric constitution and physical influences, and that in practically every case, both are at work. We could thus understand, albeit in a hazy way, how the one adult individual differs from the other, even if we were to presuppose that the ovum was exactly the same in each case; the more difficult task is to determine why one individual is like another individual, why son is like father, and this leads us to inquire wherein one ovum is different from another ovum. Two ova, side by side, look to our eyes alike, let us say: why

is one going to become an elephant and one an insect, and how comes it that the elephant is certain to have a trunk and the insect wings? Is there, in the ovum, a part of the protoplasm that is definitely of such composition that it must form a trunk and not a tail? And where is the protoplasm hidden in one cell which will determine that this particular elephant will have tusks like his grandfather, a trunk like that of his great-grandfather, and the temper of his great-grandmother? Does the ovum contain a vast accumulation of molecules of different orders and properties which have directly descended from each of his thousand ancestors? This cannot be: we can prove, from what we know of the protein molecule, that there is actually not room for them. The theory of "the continuity of the germ plasm," as it is called, which presupposes the descent from generation to generation of an infinitesimal part of the protoplasm of each, is a *physical* impossibility.

Such **"determinants"** carrying particular properties derived from one or other ancestor, which shall in due time be distributed to one or other tissue or area of the fully grown individual and shall endow that particular tissue or area with the properties seen in one or other ancestor demands, it will be seen, that every separate feature in the body, even down to the particular markings of the thumb prints (which are alike in no two individuals), shall be present in the fertilized ovum, demands, in short, that not merely the microscopic nucleus of that ovum, but the chromatin or whatever part of it conveys the hereditary characters, shall be made up of these innumerable determinants. Now, according to Weismann, these determinants cannot be simple molecules of matter, but must be molecular groups, and as we have pointed out that living matter is proteidogenous, each individual molecule must be of a size which, according to physicists, is almost visible by the ultra-microscope.[1] Regarded thus, it is a physical impossibility that the minute nucleus of the impregnated ovum can contain all the determinants demanded by this theory. If, therefore, we cannot accept the idea of determinants, is there any other means by which we can visualize the facts of inheritance and of individual variation? This biophoric hypothesis appears to us to afford the only means of explanation at present possible. The elephant ovum develops into an elephant and not into an insect because the elephant ovum is made up, in the main, of molecules of a certain average composition, a ring made up, let us say, of smaller rings each represented by A:

[1] That is, in the neighborhood of 0.1μ in diameter.

A bird ovum, on the other hand, may be made up of X rings, thus:

$$
\begin{array}{ccc}
 & X & \\
X & & X \\
X & & X \\
 & X &
\end{array}
$$

The biophoric molecules of an insect ovum might be represented by

$$
\begin{array}{c}
R \\
R—R
\end{array}
$$

These may thus differ one from another not only in general composition (as A is different from R or X), but also in number, and mode of apposition. The fundamental grouping of the molecule of all elephants is the same, thus:

$$
\begin{array}{ccc}
 & A & \\
A & & A \\
 & A &
\end{array}
$$

the biophoric molecules of the ovum of one elephant differ from those of another in certain slight modifications of one or more of the constituent parts of the ring, which may be represented as side-chains; thus for one elephant:

$$
\begin{array}{ccc}
 & A & \\
a—A & & A—a \\
 & A &
\end{array}
$$
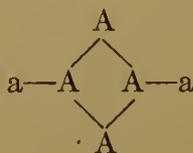
for another elephant:

$$
\begin{array}{ccc}
 & A—a & \\
A & & A \\
 & A; &
\end{array}
$$
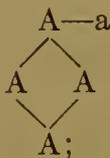
as no two individual elephants are identical or can be represented by the same formula, it is evident that progeny of any two will present a modification of the formula seen in either parent; these modifications arising by elimination, interaction, or summation of the characters represented as side-chains.

Having thus dealt with inheritance and the effects of fusion of the male and female elements in the new individual, let us now consider the modifications acquired by environment.

Acquired Modification.—Passing on to the evolution of the individual from the ovum and the differentiation of his various tissues and

organs, it must be clearly realized that when the ovum divides into two, each daughter cell has conveyed to it biophoric molecules, and that so these biophoric molecules while coincidently multiplying by the successive division and multiplication of the cells of the growing individual come to be distributed to all the tissues of the body. So far as we can see they pass to the germ cells in an unchanged condition, but in the succession of divisions which give rise to the somatic or body cells, the influences to which the successive generations of cells are exposed in the different parts of the growing embryo differ very greatly. It is due to the difference in position plus the difference in foodstuffs and physical and chemical agencies to which the cells are exposed, that the contained biophores become modified, until eventually, the modification becomes so great that instead of these biophores being able to reproduce the whole individual, they now become capable of controlling the formation of only one particular differentiated order of cell.

Following upon this, the general statement may be made that **the more pronounced the differentiation of a cell, the less is its capacity for reproduction.** Yet there are certain cells that are specialized, and can yet reproduce; but they reproduce only their own differentiated and modified kind, gland cell reproducing gland cell, muscle cell, muscle; and even this multiplication can occur only after the differentiated cell has "undifferentiated" itself again, that is, has reverted to a simpler, less differentiated stage. The cell that has become differentiated, that is, loses the characters it has acquired, and becomes a **"vegetative"** cell in form, and yet when this cell reproduces, its progeny assume once more the differentiated type characteristic of the adult cell.

FERTILIZATION

We shall take up very briefly some of the facts concerned with fertilization; that it has not hitherto entered into this text, is due to the fact that growth, adaptation, and cell differentiation can proceed without it; study of the lower invertebrate forms indicates that it is, in them, a means of **rejuvenation** of the biophore, but that among them it is not an essential to the continuance of the species through considerable numbers of generations. In its simplest phase, conjugation is the direct union of two like individuals; but even low down in the scale we begin to find a differentiation between the male and the female germ cell; the male tends to show itself motile, invasive, while the female tends to be passive, chiefly because the cell is loaded with the yolk necessary for the support of the new individual after fertilization. Of this food material the male element or spermatozoön shows little; it consists of a nucleus, a centrosome, and a small amount of cytoplasm which appears chiefly as the flagellar tail; the male cell is, in fact, of a disproportionate smallness.

From a very early date in the development of the individual ovum

the germ cells become marked off from the **somatic** or body cells; the germ cells remain rich in chromatin, none of which is cast out.

The observations of Boveri and others indicate that the cells destined to give rise to the tissues in general undergo a process of reduction of their chromatin; very possibly this process of reduction renders them incapable of being **totipotential**, *i. e.*, of giving rise to the whole individual, leaving them capable only of giving origin to a specific tissue or tissues according to their environment. Nor does it seem that the eventual sexual cells are of necessity absolutely identical in the amount of chromatin which they contain; a study of the spermatozoa, especially of insects, and of the pollen of plants, has shown recently that in any particular instance their spermatozoa may be separated into two approximately equal groups, of which the members of one group contain either one chromosome in excess of the number contained by members of the other group (**accessory chromosome**), or

Fig. 11

Fertilized   *Egg*

Undifferentiated
Embryonic Somatic
Cells

Germ cells.   *Differentiated somatic tissues of adult.*

Schema of germ and somatic cell differentiation.   (After Klebs.)
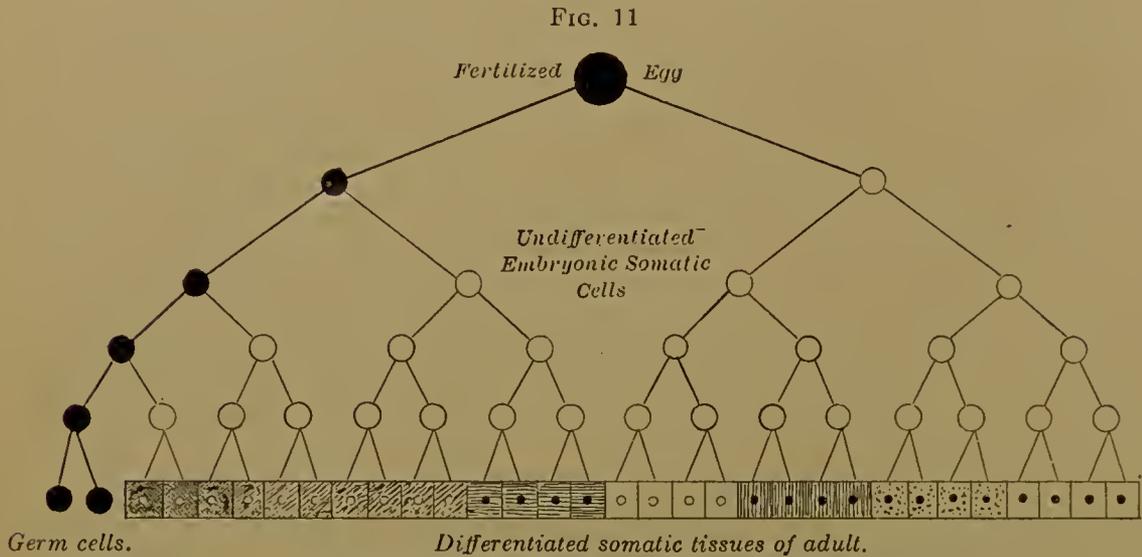
one chromosome markedly larger than the corresponding chromosome in that other group. More rarely species are encountered in which one-half of the ova possess the accessory chromosome; in this case the spermatozoa all have the like number of chromosomes, and as these species afford approximately equal numbers of male and female progeny and no other functional difference can be detected or imagined between the two groups of spermatozoa, it is presumed that the one group (that with the accessory chromosome) conveys female, the other male attributes. This conclusion is now becoming generally accepted by biologists.

We have stated that there is no reduction in the chromatin of the undifferentiated germ cells; but we have now to add to this statement, that the generation of germ cells immediately preceding the formation of the ova and spermatozoa *does* undergo a reduction of chromatin during the process of maturation, so that the mature spermatozoön or

ovum contains just one-half the number of chromosomes characteristic of the species (and it will be recalled that this is a fixed number for each species).

In the maturation of the spermatozoön, we may state briefly the fact that a pair of spermatozoa arises from a secondary spermatocyte, this in turn comes from a primary spermatocyte, this from a spermatogonium, and this from a primordial germ cell, and by the time the spermatozoön is formed it has one-half the normal number of chromosomes. The four cells derived from the primary spermatocyte all become spermatozoa, whereas, in the case of the ovum, the primary oöcyte gives rise also to four cells but only one of them becomes a functional ovum; the other three are degenerate, and are cast out of the cell as **polar bodies**, and this casting out does not occur till the spermatozoön has entered the ovum. This intracellular occurrence is for the purpose of reducing the chromosomes of the ovum, so that the ovum proper is the only one of the four which remains, and it functionates with its chromosomes reduced to one-half of the number present in the cells of the adult individual. The steps of the process of maturation of the spermatozoön and of the ovum we have omitted, but these intricate "nuclear dances" are evidently a means of ensuring that the chromatin of the original germ cell shall be impartially divided among all the daughter cells—the spermatozoa or ova; and the reduction of the chromosomes brings it about that the fertilized cell, summing the two sets of chromosomes, each reduced by a half, shall begin life with exactly the normal number of chromosomes, and these contributed equally by the two parents. The cytoplasm of the new individual (fertilized ovum) is supplied practically in its entirety by the maternal germ cell, the centrosome by the paternal. The very fact that **the nuclear chromosomes are the only constituent supplied with striking equality by both parents,** coupled with the observed fact that the individual inherits properties indiscriminately from both parents, indicate together that **the chromosomes convey the essential heritable matter.**

INHERITANCE

The importance of the problem of heredity in disease is great, and we make no apology for insisting on its consideration.

Heredity is the conveyance to the offspring of the properties of the parents and of the parental stock, so that the child inherits familial, racial, and specific characters. But this does not describe the child, because interwoven with heredity is **variation,** and this of several orders. (1) There is the variation that comes from one's course of life, as is seen in the type that is recognized as the sailor, the farmer, or the undertaker; variations so acquired are known as **modifications** and can be divided into those acquired in intra-uterine and in postnatal life. These are not heritable—included among them are **fluctuations.**

If, for example, we measure twenty members of one family we shall find them to vary in height, length of limb, etc., but the smallest member of the series may be the parent of children of height, etc., over the mean; the variations being apparently due to external environmental influence. (2) There are variations that arise because the individual is the result of **amphimixis,** *i. e.,* the fusion of the germ-plasm of two individuals who differ one from the other. The child cannot, on this account, be an exact copy of either parent, but must show variation from each. (3) The molecules of germ plasm of two parents are so complicated that their interaction never produces the same result twice; even the thousands of fish from the same spawning differ from one another, so that, finally, we must admit that the bio-phores of the parent which supply the germ cells are prone to variation during the individual life of the parent.

The Different Forms of Inheritance (*i. e.,* **Heredity Plus Variation**).— The properties possessed by the individual are these:

1. **Individual,** *i. e.,* those peculiar to the individual, and not recognizably inherited.

2. **Parental,** *i. e.,* properties possessed by and peculiar to one parent and obviously inherited from that parent.

3. **Familial,** *i. e.,* properties possessed by and peculiar to the family of one parent.

4. **Racial,** *i. e.,* properties common to a particular race.

One may go farther, and indicate that the individual has specific or *ex specie* properties, such as those that distinguish him as a human being from an ape, and even *class* and *order* distinctions.

We see that there is an ascending order of fixity in these characters, viz., that, dealing with man, his vertebrate characters are more firmly imprinted on him than his mammalian, his mammalian than his human, his human than his racial, and his racial than his familial characters, and so on. His least imprinted characters (*i. e.,* his individual characters) are those most liable to change, and among them the ones he. has possessed longest he gives up least readily.

Racial Characters.—To go no farther back than this, everyone is familiar with racial differences, evidenced by the color of the skin, the shape of the skull, and the stature. In more strictly pathological fields, one may recall the differences in reactive power to certain microbic diseases; thus the Japanese and the native Austrian cattle are less susceptible to tuberculosis than most others; one race of Algerian sheep can scarcely be inoculated with anthrax; negroes and American Indians are highly susceptible to tuberculosis, and so on. In non-microbic diseases, it is a matter of common knowledge that the Hebrew is prone to diabetes; the French, to functional nervous diseases; the English, to gout, and the American to disorders of digestion. To say that these are due to the particular mode of life is precisely what we wish to indicate: primarily they must be regarded as the outcome of particular environment.

Familial Characters.—Not only do the members of a family tend to resemble one another, but there are certain distinctive traits that are found in many successive generations—a peculiarity of stature, a shape of some special part—"that thou art my son," said Falstaff, "I have partly thy mother's word . . . . but chiefly . . . . a foolish hanging of thy nether lip"—or a morbid condition such as **albinism** (deficiency of cutaneous pigment), **color blindness, hemophilia** (liability to excessive hemorrhage as a result of insignificant injury), or actual malformation such as the possession of an extra digit. When we consider that such peculiarities as the last have been traced in a family for centuries, despite the constant introduction of new blood, it is evident that these are **dominant** properties possessed by the germplasm of particular strains. The further study of some of these characters reveals the fact that there are some of them which appear in one sex and are transmitted by the other.

Sex-limited Inheritance.—Hemophilia, for example, rarely appears in the females of an affected family, but frequently in their sons. Characteristics may skip a generation or more, so that the appearance of such in children whose parents were free from but whose grandparents or preceding forebears were affected by them, is designated **atavism.**

Parental and Individual Characters.—The characters that descend from the parents to an individual may be **blended,** that is, he may possess a mixture of the paternal and maternal features, intermediate between the two, or they may be **particulate,** that is, he may resemble one and not the other. There are certain parental characters that ordinarily cannot blend, and sex is the most striking of these. Less important is such a character as the color of the eyes; one parent may have blue and one brown eyes; the children generally do not show an intermediate color, but either blue or brown eyes, exceptionally one brown, the other blue. One of the two parents, in properties that are unlike or antagonistic, is apt to be **dominant,** and the other is then **recessive.**

Mendel's Law.—Without going deeply into the particulars of inheritance in the matter of antagonistic characters, we shall indicate the exactness with which nature works, as it was observed by the Austrian monk Mendel, whose work has in this century been revived. Let us take for example, as he did, the flowers of the pea; some strains have white flowers, others colored. Color is a positive acquirement, and whiteness most often means latency or loss of this acquirement. If now red and white flowers are crossed upon one another, the hybrids which result follow a law in regard to manifesting this particular character and the first generation is red. The red color is dominant, and there is no indication of the white color—the white being recessive. But in this experiment the white color is only latent, and this fact will appear if this first generation (red) be allowed to fertilize itself; among its progeny one-quarter of the individuals will be white, that is, will show the recessive quality. If this white individual be self-fertilized again, all its progeny will be white. Now, of this second generation

4

FIG. 12
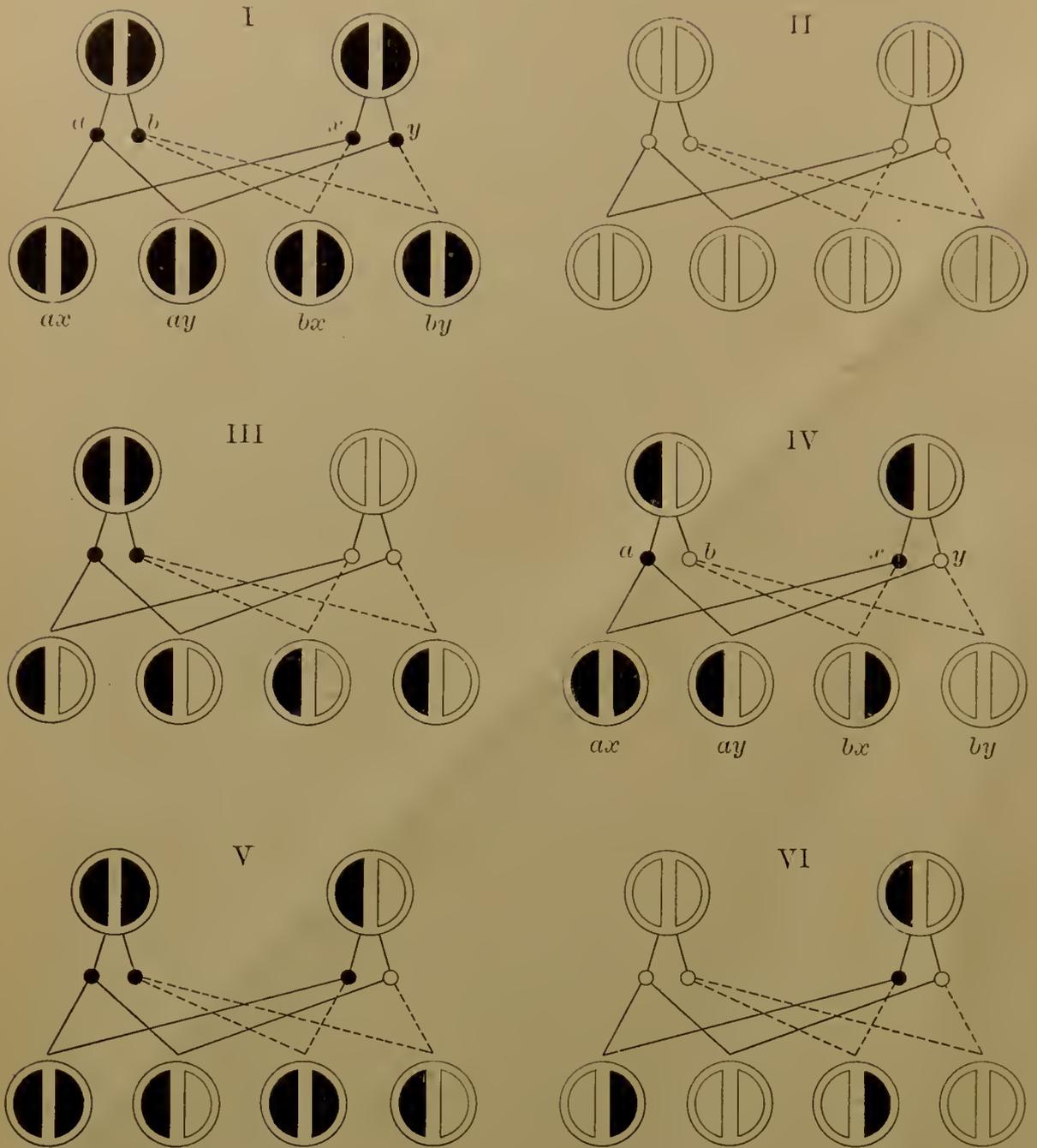
Schema showing the orders of inheritance of a unit character according to the Mendelian Law. A dominant character in either parent is represented by black. This dominance may be duplex, as in I, where the character has been received from both parents, or simplex as in III, where the character is conveyed from one parent only. All individuals receiving thus the dominant character will be of dominant type whether they and their cells be of simplex or duplex constitution. The germ cells a, b, x, y, in the duplex individuals are all of the same order; in simplex individuals one-half, a or x, convey the dominant character, one-half, b or y, convey the recessive character. The a matings are represented by unbroken, the b matings by dotted lines.

I. Mating of two pure, duplex dominants. *Result:* All the offspring duplex dominants.

II. Mating of two pure, duplex recessives. *Result:* All the offspring pure recessives.

III. Mating of duplex dominant with duplex recessive. *Result:* All the offspring simplex dominant (or heterozygotes, Mendel's F_1, generation in hybridization).

IV. Mating of simplex dominant with simplex dominant. *Result:* Offspring in ratio of one pure or duplex dominant, two simplex (dominant), and one pure duplex recessive (Mendel's F_2 generation).

V. Mating of duplex dominant with simplex (dominant). *Result:* Offspring one-half duplex dominant, one-half simplex (dominant), pure recessive, one-half simplex (dominant).

VI. Mating of pure or simplex recessive with simplex (dominant). *Result:* Offspring one-half.

of four plants (three red and one white), of the three red, one, when self-fertilized, will give only red progeny, the other two of this second generation will have the characters of the first generation of hybrids,

Fig. 13
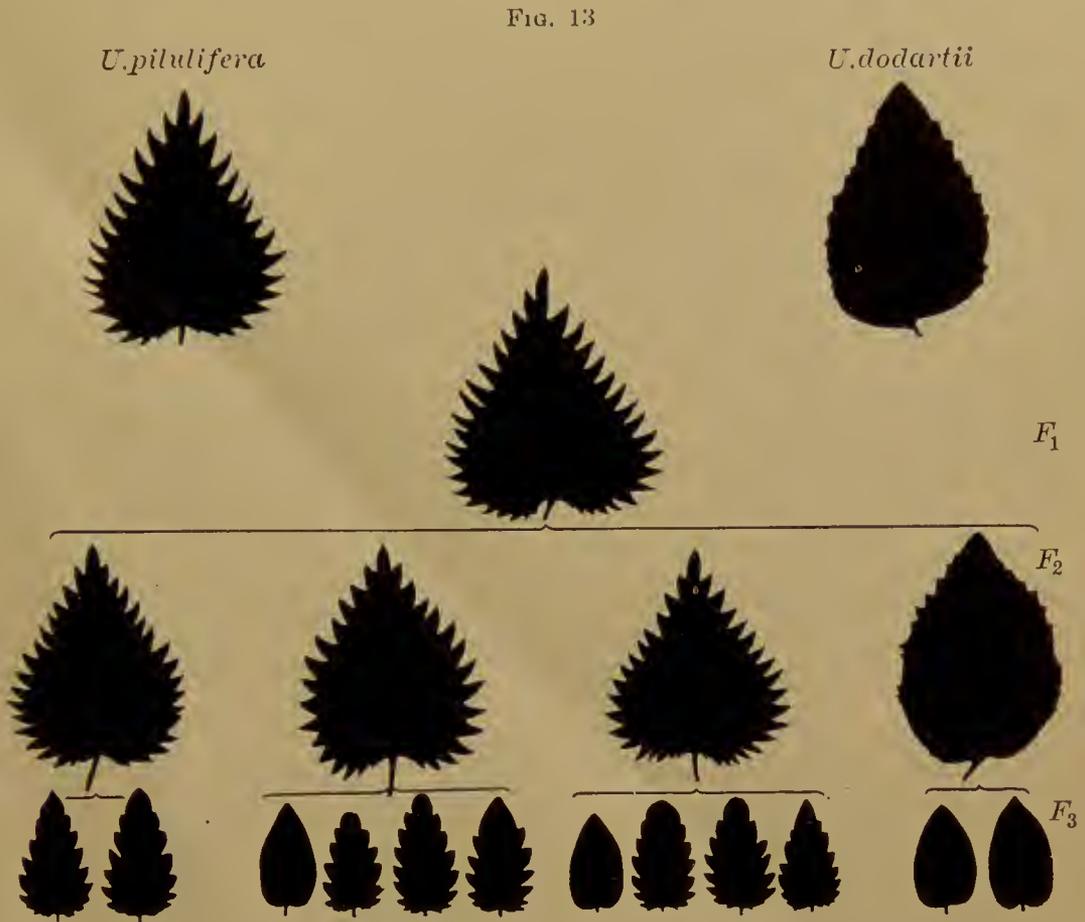
Leaf characters of hybrids of *Urtica pilulifera* and *U. dodartii* (Correns): F_1, of first hybrid generation, F_2 and F_3, of second and third self-fertilizations. The dentate character of the leaf edge is seen to be a dominant property.

Fig. 14
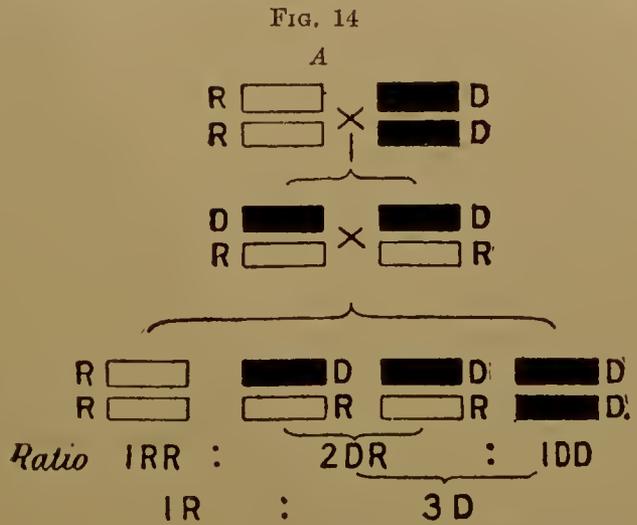
Schema of Mendel's law for a single pair of "antagonistic" properties: *A*, the results of hybridization of a pure dominant (*D*) with a pure recessive (*R*) form. (Bateson.)

that is, they will give rise in the next generation to one dominant, one recessive, and two hybrids that again will produce this same percentage of dominants, hybrids, and recessives. This will be understood better from Fig. 13.

The formula may be set down as follows: if D represent a plant with the dominant red and its germplasm and R one with the recessive white and its germplasm, then the first generation of crosses of D and R will all be DR, and if these DR individuals be crossed the result will be $x (DR + DR) = x (DD + 2DR + RR)$, or in other words, a dominant crossed with a recessive gives in the second generation, as regards this one particular feature, one dominant, two hybrids, and one recessive, and of these, each pure dominant crossed with a pure dominant can give nothing but dominants, each recessive nothing but recessives, and each hybrid the same proportion of dominant, hybrid, and recessive.

The essential point to be grasped here is that while one property dominates, the other is only latent, and may show itself in the absence of the dominant property or mingled with it in a blend. The law, too, does not hold in the crossing of distinct species, and we quote it only to indicate how accurate a basis even with our imperfect knowledge we have for the consideration of problems of heredity in the human species. This is the observed law of appearance of one differential feature; where the two mating varieties differ in more than one set of features, the formula becomes more and more complicated the greater the number, although constantly the members of the first generation exhibit dominant characters, the recessive only reappearing in the second generation. We must, however, refer those interested in this subject to one of the many works devoted to the exposition of the Mendelian law.[1]

Atavism.—This is the appearance in a given generation of traits not present in the parent but characteristic of earlier generations, and is seen to be in accordance with Mendel's law. If, however, we find traits appear which are characteristic of an earlier state in the phylogeny of the species, we designate this **regression**. In reversionary inheritance or **regression** we have always a return to a lower type— a development not completely up to the present type but attaining a stage characteristic of an earlier period in the development of the species. An example of such is the appearance of a microcephalic child or of a child with indications of persistent gill clefts; not all such cases are true reversion; very many are the results of intra-uterine arrest of development. A perfect example of regression is found in Darwin's experiments and those of others, in which when widely differing breeds of pigeons were crossed, the progeny, disregarding, as it were, all the recent acquirements, have appeared exactly similar to the form of wild pigeon from which all the different varieties took their origin. One seems to see, from time to time, the offspring of parents of widely diverse stocks showing this reversion to a lower type.

Familial Degeneration.—This is a form of degeneration which we ascribe not to the interaction of two antagonistic germplasms, but to a defect in one or both induced by toxic influences, which modify

[1] Among these may be noted: Bateson, "Mendel's Principles of Heredity," Cambridge Univ. Press, 1913; Darbishire, "Breeding and the Mendelian Discovery," 2d Edit., Cassell & Co., 1912; and Walter, H. E., "Genetics," Macmillan Co., 1913, the last being an excellent presentation of modern views.

the constitution of the parental germ cells. The class so produced we designate **degenerates**—the product of those leading vicious lives. The degenerate is of poor bodily development, the brain is smaller than normal, its convolutions less marked, there is little capacity for prolonged thought, and a lack of moral sense—in all these points, there is a resemblance to a lower, less-developed race of our species. Such are apt, in turn, to produce children who are idiots, stillborn, or monstrous.

Spontaneous Variation; Mutation.—We have previously been dealing with conditions appearing in the ancestor, and conveyed to the offspring; but there appear in the offspring conditions and relationships that are new to the stock, that have *arisen,* and these are called **spontaneous variations.** The clover has a tri-partite leaf, but a four-leaved clover is occasionally found, or even five- and six-partite leaves; this does not mean that the ancestors of the clover plant had a four-, five- or six-partite leaf. We describe this as a spontaneous variation. We find the same thing occurring in the human species; supernumerary mammæ, fingers, or vertebræ occur, and, once present, tend to be inherited. The first of these in any series to happen was a mutation, a spontaneous variation; and botanists have been able to show that a new variety will suddenly arise, and, self-fertilized, remain true to its new type. Some say that evolution works in this discontinuous way, and that a new variety or new species does not come by slow gradation but by sudden genesis. It may be, of course, that we have here an example of **cumulative inheritance;** that is, where a blend, instead of showing a feature intermediate between two differing parental features, shows this feature exaggerated in the direction of but far beyond that feature in one parent; but we have also to remember that mutations have been obtained by various physical effects, *e. g.,* the influence of chemical agents acting upon ova.

The Theory of Inheritance.—The consideration of fertilization and the processes that precede it leads us to suppose that each parent contributes one-half to the germ cell of the offspring; half the chromosomes are of paternal, half of maternal origin, and the heritable material is evidently in these chromosomes and any theory of inheritance must deal with the chromosomes and their constituents—that is, with the biophoric molecules conveyed in the chromosomes.

We may group the various forms of inheritance, most of which have been referred to, as follows:

(*A*) Presenting itself also in the offspring:

1. **Dominant,** wholly replacing the corresponding but divergent feature seen in the other parent.
2. **Blended,** this particular feature in the offspring being intermediate in character between that exhibited in the two parents.
3. In **mosaic** form, in certain cells the paternal, in others the maternal feature being dominant.
4. **Blended and excessive,** the feature being more pronounced than in either parent.

(*B*) Unrecognizable in the offspring:

    1. **Recessive**, and replaced by corresponding feature derived from the other parent, but as such latent, capable of reappearing in later generations.

    2. **Absent**, wholly wanting in subsequent generations, the absence being due either:

        (*a*) To casting out of an inherited condition, or

        (*b*) To the feature seen in the parent being an acquirement and not an inheritance.

Or, on the other hand, considering the individual, we note that as regards any particular feature or group of features, there may be:

(*A*) *Normal Inheritance:* The offspring not being in this respect advanced beyond either parent, but at the same time not fallen behind.

(*B*) *Progressive Inheritance:* The offspring being advanced beyond the more advanced of the two parents and exhibiting either:

    1. Excessive development of the condition or conditions already observable in one or both parents, or

    2. Spontaneous variation (mutation), *i. e.*, the appearance of conditions not previously noted in either parent or either parental stock.

(*C*) *Retrogressive or Reversionary Inheritance:* The offspring reverting as regards any feature or group of features to a lower stage in the phylogeny of the species.

(*D*) *Non-inheritance:* Apparent or actual.

It will be seen that qualities conveyed by the parental biophores may be retained even if in a recessive, latent condition. The fact that the Mendelian hybrid after a number of generations can produce a purely dominant or purely recessive individual shows this, and conjugation cannot, therefore, be a chemical union of two biophores with a resulting new biophoric substance. Nor can there be separate biophores representing each individual ancestor. The following is our conception of the process of conjugation between parental biophores in the fertilized ovum. We may picture these biophores as lying side by side in a common cytoplasm from which they extract and to which they give ions, so that some side-chains are being built up and some dissociated. Of these side-chains many are identical, common to the molecule of each parent; these possess the fixed characters of the species, the race, the order; others are unlike, and these evidently mark the individuality of each parent. The molecules and their side-chains will have certain affinities for the side-chains of the molecules of the germ-plasm of the other parent, and with the constant interchange which we consider the essence of the life process, some of these will be incorporated into the ring and others will be cast out completely. There will be a kind of contest between the parental biophores, and as a result a re-arrangement, so that the characters represented by side-chains with strong affinities will appear in the offspring, and characters

represented by side-chains with weak affinities will be cast out and will
not appear, nor even exist in the new germplasm. Without increasing
the number of individual molecules, this semichemical process allows a
constant number of biophores to bear properties of many generations.

Fig. 15
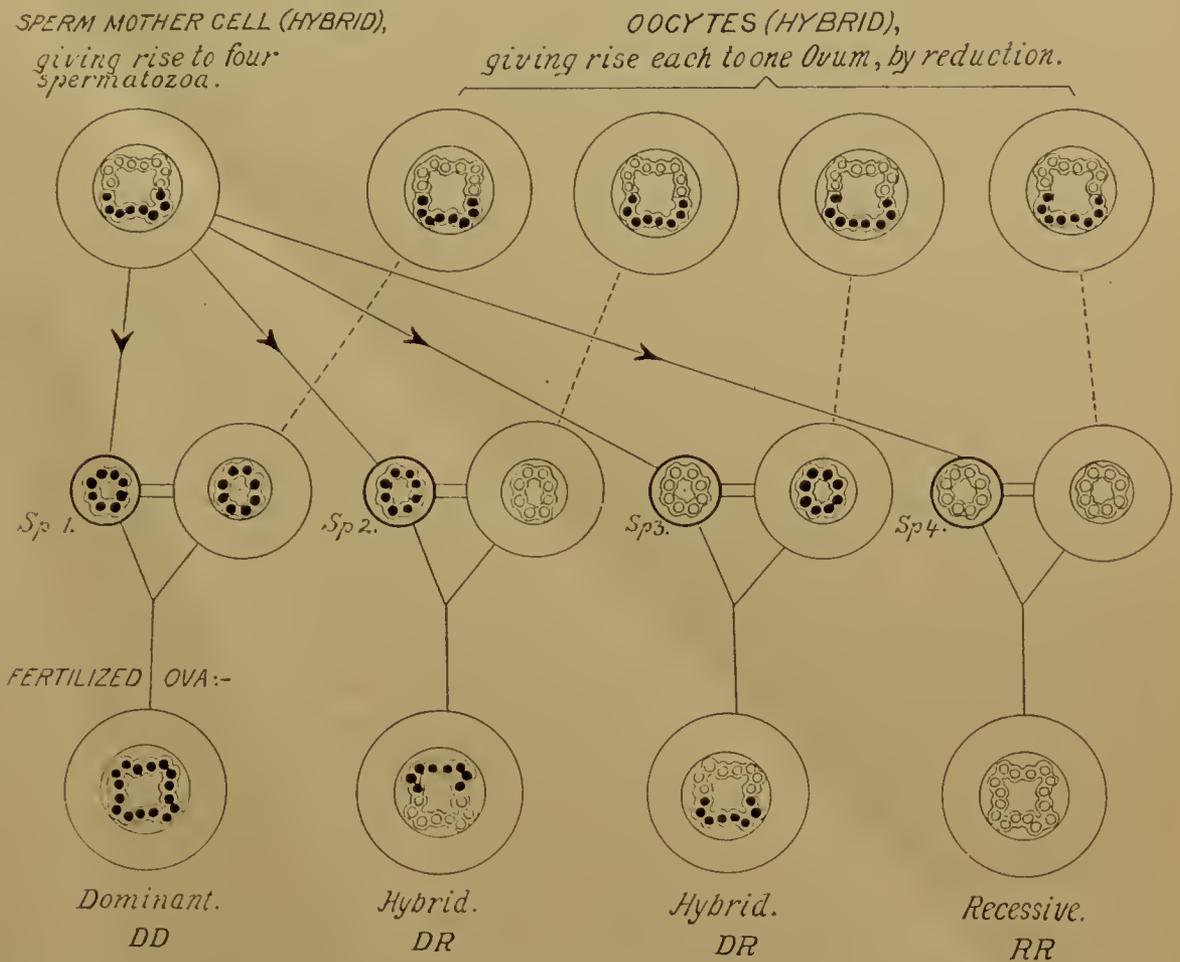
Schema to illustrate Mendel's law regarding the second hybrid generation, to illustrate the effects
of reduction of the chromosomes in oögenesis and spermatogenesis. Each germ cell (first row) is
originally provided with chromosomes of paternal (black) and of maternal origin (white). The
existence of the law demands that in the process of reduction the ovum and the spermatozoön (second
row) become provided with chromosomes (and biophores) that are of either paternal or of maternal
descent, but not of both; although, as above noted, the biophores may in their growth and develop-
ment have attracted side-chains formed primarily by the opposed order of biophores, to the exclusion
of those originally belonging to them.

If then one considers a scheme such as that afforded by Fig. 15
it will be seen that in the process of reduction undergone by their
chromosomes the mature oöcyte and spermatozoön each undergoes a
process of casting out of chromosomes derived originally from one or
other grandparent. As the same order of chromosomes is not cast
out in each ovum and spermatozoön, the data obtained from Mendelian
experiments show us that the casting-out process evidently in each
case involves the biophores derived from one or other of the grand-
parents. With promiscuous mating of ova and spermatozoa, this
alone can give us the Mendelian formula.

We think such an explanation suffices to show how hereditary characters of many generations may be conveyed in a small number of complex molecules; how these molecules may be altered (being proteidogenous molecules) by amphimixis (that is, mingling with other molecules) and by environment (that is, by interchange with the surrounding cytoplasm); how they may lose entirely certain side-chains, and thereby certain properties, even if these are hereditary.

The Inheritance of Acquired Characters.—Are acquired characters transmitted? is a long-argued question. Contrary to the dominant teaching of the morphologists we think that some few, but by no means all, may be. It has been indicated before that we picture the biophoric molecule as in interaction with the cytoplasm that surrounds it, giving up to it and taking from it ions, and this in its turn interacting with the surrounding medium, the lymph. The biophoric molecule weaves into itself, thus, some flavor of its surroundings, and can transmit whatever it has. It will be evident that there are some kinds of acquirement that can be transmitted, and some that cannot. The so-called "maternal impression," by which a pregnant woman seeing or imagining something which mentally impresses her, is supposed to transmit it to the offspring she is carrying, is a myth. "Use acquirements" are not transmitted; by this we mean that the blacksmith's arm is not reproduced in an unusually large biceps in his son. We have not as yet definite evidence that acquired immunity can be transmitted, although the offspring can obtain immunity during intra-uterine growth; to prove that immunity can be transmitted, it would be necessary to have only the male parent immunized, and to find the progeny so immunized. It might almost be predicted that immunity would be transmitted according to the Mendelian law, some of the progeny being immune, others not. Mutilations, loss of limbs, etc., are not transmitted. On the contrary, there is a series of retrogressive changes in the tissues, the result of toxic influence, which does seem to be able to affect the progeny. For example, it seems as if the drunkard begets children who are the worse for his habit; we need scarcely point out how difficult it is to prove this statistically, because there are so many factors to consider, such as these: the mother, being sound, may dominate the offspring, and the child be normal; if the child be abnormal, can we say that the father's alcoholism was the prime cause? May it not be that the father's alcoholism and the child's weakness are alike expressions of an hereditary taint in previous generations of the father's family? Or, again, may not the child's incapacity be due to the misery and want that so often go with alcoholism in the homes of the poor? Nevertheless it has been proved experimentally by treating the male guinea-pig with alcohol that his progeny is defective; where not stillborn it is liable to succumb easily in early life, or, surviving, is stunted and stupid. What is more, Stockard has shown that the offspring of this second generation of guinea-pigs are similarly stunted and stupid. It is not easier in tuberculosis and syphilis; but in all

these instances, as well as in poisoning by such chemicals as lead, series of cases do present a high percentage of monstrosities, still-births, short-lived and mentally defective children. This, it is true, is not the transmission of characters acquired by the parent: at most it is proof—equally important to us as medical men—that conditions affecting the parent may simultaneously influence the germ cells and so tell upon the next generation. The germ cells of the parent are capable of modification by modifications in the constitution of the parental blood and lymph. The only true inheritance of acquired conditions that we can comprehend is in connection with the organs supplying an internal secretion. If such an organ be so affected in the parents as to produce an internal secretion altered either in amount or composition, there are indications that the secretion circulating in the blood may affect the germ cells. In this way we occasionally observe that parents with acquired goitres have goitrous progeny. Whether we accept this evidence or not, whether we accept or deny that there is a true transmission of acquired conditions, it is all-important for us to realize that infections and intoxications seriously affecting the parental tissues may simultaneously exert a deleterious influence upon the germ cells and, modifying them, may lead to the offspring being defective. As the brain is the most highly and most recently developed of all the tissues, defective development is especially apt to show itself by imperfect mentality and mental instability.

CHAPTER II

THE CAUSES OF DISEASE

In the cell, the organ, or the individual, any deviation from the normal is a pathological condition.

The **normal** is the state, customary to a series of individuals, in which they perform their functions easily and unconsciously, and this constitutes health; this normal, naturally, will not be fixed, but will be a varying state, and will be only arbitrarily separated from the state on which it borders, viz., disease.

The diseased state arises in the individual (or the cell or the organ) either from the parent, in which case it is **inherited,** or as a result of some influence after the genesis of the individual, in which case it is **acquired.** The genesis of the individual is the moment of fecundation of the ovum; and any pathological state that is entered upon after this, is acquired, unless it be the result of qualities which were in the germplasm of one or other parent or which arose by the junction of these. If it be such a result, the pathological condition is an inherited one, even though the appearance of the pathological condition be delayed for years (as is most often the case with gout); an example of this, indeed, is "old age," an inherited pathological condition which the individual has potentially possessed all his life. On the other hand, an acquired pathological condition may arise while the embryo is still but a few weeks old, and this, arising from an intra-uterine disturbance, is a "congenital" but not an "inherited" pathological condi-

tion. In differentiating between inherited and acquired conditions, it is necessary to date the life of the individual from his beginning and not from the comparatively accidental period of his birth, which, even among mammals, is a varying point of time. Yet since birth is the most important change of environment that the individual undergoes, we may distinguish acquired pathological conditions as either **antenatal** or **postnatal**, and those few which are due to something happening to the individual at the moment of birth as **parturient**.

While pathological states may be separated, as above, into groups which differ from one another in the *period* in which the causative agent acts, it is necessary to indicate what these causative agents are, and it is a perfectly sound method to consider them as **direct** and **predisposing**. Fifty years ago, physicians knew many predisposing causes but few direct ones; today we are finding out one direct cause after another (witness the specific microörganisms), and we tend to lose sight of the predisposing or assisting causes. For example, many individuals carry in the throat the germ which we count the direct or exciting cause of pneumonia; the assisting cause apparently must act before a man is attacked by pneumonia, and this assisting cause is not the same in all cases, and frequently is entirely intangible; we hide our ignorance behind the term "lessened resistance," and although this may be as yet only a name, we must not fail to keep in mind that assisting, indirect causes exist. It even happens that the same agent may be at one time an exciting cause and at another a predisposing cause; such is cold, which at one time freezes a tissue, and at another, paves the way for the inroad of pneumonia.

Predispositions are thus the result of the presence of assisting causes, or of the absence of preventing properties. When we say that there is in an individual a predisposition to tuberculosis, we mean this. We have in our mind a series of generations of a family in which cases of tuberculosis arise more frequently than in the same number of individuals, taken at random; in this family we note certain peculiarities of build of habit of life, of constitution, which we suspect have a relation to this increased tendency to tuberculosis. An individual possessing all these peculiarities may, it is true, escape tuberculosis, but his chance of escaping it we hold to be less on account of his possessing these peculiarities and the history of increased incidence of tuberculosis that has arisen in conjunction with them. We say that such a person possesses a **diathesis**: *a diathesis, therefore, is an inherited constitutional state which renders the individual predisposed to or liable to be affected by a particular disease or group of diseases.*

Diseases and Affections.—Here, for clear thinking and sound treatment, a word must be said against the prevailing lax employment of the word **disease**. Too often we speak of a patient as affected with heart disease or kidney disease, and doing this almost inevitably our thoughts turn toward the employment of drugs and other means of acting specifically upon the particular organ with the underlying idea that if we relieve

the affected organ we can cure the individual. Nine times out of ten this is false procedure: nine times out of ten we can by this means at most temporarily ameliorate certain symptoms. Nine times out of ten, and not oftener, the morbid state of an important organ is the outcome of disease originating elsewhere, affecting the body in general, but especially telling upon some one organ. Thus, for example, most often heart "disease" is the result of either recurrent rheumatic infection or of that condition which, for want of a better term, we call general arteriosclerosis; and today we would think the man a fool who sought to cure a syphilitic rash by local instead of general anti-syphilitic treatment directed toward the destruction of the treponema throughout the body; so our duty is, when possible, to determine the primary and underlying cause of disease, to speak and to think not of heart disease but, for example, of acute rheumatism affecting the heart. For clear thought, therefore, it is well to distinguish between diseases and affections, to speak of primary diseases and secondary **pathies**—of cardiopathies, nephropathies, hepatopathies[1] and the like.

INHERITED PATHOLOGICAL STATES

It may be repeated that the results of all the morbid influences which bear upon the foetus in the womb are acquired; **mutilations** *are never inherited*, and the statement may be safely made that infectious disease in the parent *cannot be inherited* by the child, although it may be communicated to the child *in utero*. The cases in which children are born with tuberculosis, syphilis, smallpox, or other such diseases, are cases in which the child has contracted the disease while in the mother's womb. These diseases are transmitted by some germ, known or yet to be discovered, and to say that they could be inherited means that the germ must be in the spermatozoön or the ovum as a foreign body, for we cannot imagine it as being incorporated with the protoplasm of the spermatozoön or the ovum and retaining its individual power to cause disease; but it is not conceivable that a minute germ cell with a bacillus or a protozoön inside could perform the delicate function of fecundation. As readily should we look for good time keeping in the hatter's watch, which, it will be remembered, was full of the best butter. It is true that in animals where there is a large yolk with the egg, the yolk may become infected almost immediately after fertilization, as happens in the ticks that cause Texas fever, and as is seen in the eggs of experimentally tuberculous hens; but the human ovum is so minute, and so free from yolk that infection of it can scarcely happen at so early a moment; nor if it could so happen, would it lessen the truth of the statement that it becomes an example of a pathological condition, acquired, not inherited.

[1] πάθος, suffering: καρδία, the heart: νεφρός, the kidney: 'ηπαρ, the liver.

This matter of acquirement as distinct from inheritance especially interests us at the present time in connection with syphilis and tuberculosis. We would like to make the distinction between **congenital** syphilis and tuberculosis respectively and **parasyphilitic** and **paratuberculous** lesions. We have evidence, that is, that without suffering from the actual infection—without congenital transmission of the germs of these diseases—the offspring of the syphilitic and tuberculous parent may exhibit certain defects of development due to the syphilitic or tuberculous **intoxication** and deterioration of the germ cells. We have to admit, however, that the abundant employment of the Wassermann test during the last few years has shown actual infection of the child to be so frequent that at the present moment it is difficult to determine whether certain stigmata, such as "Hutchinson's teeth," which we used to regard as parasyphilitic, are not truly indications of intra-uterine infection. There are debates, likewise, covering the frequency of intra-uterine transmission of the tubercle bacilli. Hence today parasyphilis and paratuberculosis are terms to be used with great caution.

Where a parent is constitutionally diseased we may have the effects of that disease manifested in various ways, depending upon the extent of the disease in the one parent, and the relative activity of the germ plasm of the other parent:

1. *Sterility,* no offspring being produced.

2. *Imperfect development* of offspring, giving rise to (*a*) intra-uterine death, or (*b*) physical malformation, (*c*) lowered resistance, of so frequent occurrence as to be called "paraspecific" in its nature.

3. Imperfect development of offspring, *appearing later than the succeeding generation.*

4. *No apparent effects.*

The Inheritance of Abnormalities Passed Down from Previous Generations.—If abnormalities can be transmitted, it will readily be understood that the oftener they appear in a series of progenitors, the more certain they will be to exist in offspring. Without attempting to explain its origin, an abnormality becomes in this way more fixed, more likely to appear after each appearance; such are polydactylism and hypospadias. It is not yet evident if color blindness and hemophilia be such *anatomical* inheritances, but they probably are. To go a step farther, there are nervous imperfections that appear to us merely as predispositions or tendencies, that are really dependent upon the anatomical lack of certain nerve-cell groups; some of these nervous imperfections are now classed as instances of **abiotrophy** (Gowers), a premature exhaustion of nerve-cell groups, but this failure in complete function may really have a strictly anatomical, if yet unseen basis.

Diatheses.—While we deny the transmission of infectious disease by the germplasm, we admit that an attack of infection may modify the next germplasm for better or worse, in the direction of giving the

offspring greater protection or greater liability. We are unable to localize this quality, and probably we shall never understand what it is, but as a result of it there is the existence of "racial" diatheses, or, stated otherwise, the absence of racial immunities. The Hebrew has a certain racial freedom from tuberculosis, and a racial liability to metabolic disturbances such as diabetes and, in the female, obesity; the white rat has a racial freedom from anthrax, and many carnivorous animals from evil results of septic wounds. A man's offspring inherits from him qualities which render it liable to or exempt from a certain disease just as it inherits a likeness of feature. We cannot take two needles and tease out of an ovum the particular piece of protoplasm that possesses these potentialities; but there is something actual in the germplasm, in the relation of one part to another, or in the molecular grouping, that constitutes a real basis for the "diathesis"; and when we go farther and find that diseases such as hysteria and epilepsy, which we frequently name **functional** diseases, are inherited, we realize that there may be a chemical and cellular basis for the transmission of "nervous diatheses"; but if we cannot find the organic change in the tissues of the diseased individual, it is yet more futile to attempt to find it in the germplasm.

INTRA-UTERINE AND PARTURIENT CAUSES

Morbid Conditions Acquired in the Womb.—Widely varying results accrue from influences acting upon the embryo or the fœtus, and although the morbid states will be discussed from the standpoint of causes rather than results, it is well to indicate what these results are.

1. Death of the embryo, with absorption or "blighted ovum" or abortion, the fœtus being imperfect: or premature labor.
2. Monstrosities.
3. Malformations of excess or of defect.
4. Impaired vitality, with imperfect development, without gross anatomical change: (*a*) General—infantilism, etc. (*b*) Systemic—especially of the nervous system.
5. Cachexia.
6. Infection.
7. Traumatism.

On the other hand, if we classify the causes that lead to the above results, we find that there are certain influences acting on the embryo, as follows:

1. Physical and mechanical causes, including injuries.
2. Malnutrition.
3. Intoxications.
4. Infections.

1. **Physical and Mechanical Causes.**—By violent shaking, the eggs of certain invertebrates in the four- or eight-celled stage may have the individual cells wholly separated, with the result that each cell may

give rise to a complete individual, or partly separated with the production of double or multiple monsters. Constant vibration may produce abnormalities, presumably by disturbing the relation of the molecules one to another; but we know of no parallel facts in the case of the mammalian embryo. We do know, however, that when the amnion is incomplete there may be unequal pressure brought to bear upon the embryo, or adhesions may form between embryo and amnion, producing malformations; and that occasionally, the movements of the fœtus may result in knots of the cord, so that limbs are thereby amputated. Fœtal fractures occur without any external traumatism, and are, in such cases, due to abnormal fragility of the bones.

2. **Malnutrition.**—Beyond the simple statement that malnutrition of the mother may cause puny development and weakly constitution of the child we cannot go. Definite anatomical defects are probably not so caused.

When there is disease of the placenta also, nutritional defects in the fœtus are very readily seen, because oxygenation of fœtal blood is imperfect, and fœtal death may ensue. Even where a monochorial twin pregnancy exists, that is, where there is a common chorion and fused placenta, the more vigorous twin may usurp more than its share of the placental circulation until finally it drives its blood by anastomosing vessels into the umbilical artery of its weaker companion, whose heart fails to develop, and whose weak circulation gives rise to œdema of its tissues; the feebler twin may thus be born acardiac (without a heart).

3. **Intoxications.**—It has been experimentally proved that poisons, such as lead, mercury, arsenic, carbon monoxide, morphine, and alcohol pass through the placenta and can be found in the fœtal tissues. In lead poisoning the offspring is frequently idiotic, imbecile or epileptic; and it has been shown that where the mothers were exposed to lead absorption, 88 pregnancies resulted in only 12 healthy children; in 32 pregnancies where the father alone had been exposed to lead poisoning only 3 of the offspring survived their third year. In a large series of alcoholic mothers, it was found that the percentage of abortions, stillbirths, and children dying before the third year, was nearly two and one-half times as great as normal. Where the mother became progressively a victim to alcohol, the high death rate of the later offspring and the lowered vitality of the living children became more marked.

4. **Infections.**—When the mother suffers from an infectious disease, the absorption of toxins by the child in the womb is often sufficiently great to result in its death, a state of affairs identical with the cases just described. But occasionally, though not often, the infective agent finds its way into the fœtal tissues, and the child is born with the disease which afflicted the mother. With doubtful cases carefully excluded, there yet remain instances of the transmission in this way of syphilis (the mother alone being infected), tuberculosis, varicella, variola (though not vaccinia), measles, scarlatina, erysipelas, rheumatic fever,

typhoid fever, cholera, epidemic cerebrospinal meningitis, influenza, relapsing fever, malaria, and yellow fever. The explanation of these cases is probably that a gross lesion of the barrier between the maternal and foetal circulations occurred, and not that the causative agent "filtered through."

The Effects of Placental Disease upon the Foetus.—The placenta is essentially a part of the foetus, and is a mass of finger-like projections (the villi) of the outer coat of the foetal sac into the uterine wall; the epithelium of these finger-like projections has great phagocytic power, and absorbs the tissue of the uterus until each finger-like process comes to lie in a large blood sinus of the maternal organ. Each finger-like process contains a vascular loop and the foetal blood flowing in this loop exchanges oxygen and other diffusible materials with the maternal blood, through the wall of the villus.

It is obvious that these finger-like processes, with their phagocytic power tend to weaken the walls of the maternal sinuses, so that hemorrhage is apt to occur; in fact, normally, hemorrhages do occur, forming accessory sacs into which new villi make their way; with heightened maternal blood pressure or with maternal tissues ill-nourished, extensive hemorrhage may occur. Such blood being effused gives no oxygen or nutrition to the foetal blood, and by its very presence prevents, wholly or partly, the normal circulation, so that the foetus may perish from asphyxia. This is a cause of premature labor and stillbirth. If the hemorrhage be not sufficiently severe to bring this about, it will, nevertheless, be followed by thrombosis, and finally, by fibrosis of the areas affected. This will reduce the area available for the nutrition of the foetus, which will necessarily be impaired. Impaired nutrition of the foetal structures may be exemplified in disease of the finger-like processes, the villi themselves; they are at times œdematous, cystic, or they may become partly fibrosed, any of which conditions may give rise to pressure upon the vascular loops, with consequent lessening of the efficiency of the circulation. The nutrition and growth of the foetus thus appear to depend directly upon the amount of good placental tissue, and the more numerous the villi, and the more active they are in phagocytic properties, the better will be the nutrition and the greater the growth of the child.

Of infections of the placenta the most important is **syphilis**. In this, there is cellular overgrowth of the villi with œdema, and both of these features tend to increase the size of the placenta. Thus in syphilitics, the placenta may weigh half as much as the child, although in normal persons its weight is about one-fifth. A puny child, of course, is partly responsible for this altered ratio. Multiple small abscesses are also frequently found in the syphilitic placenta, and the co-existence of these with the changes mentioned above is characteristic. To the eye, the placenta is large, pale, and may have yellowish-white fibroid areas. A further character in syphilis is the leukocytic infiltration of the umbilical cord.

Hydramnios (excess of amniotic fluid) often arises in syphilitics, although cardiac defects of the fœtus may also cause it; hypamnios (deficiency of amniotic fluid) is also sometimes a result of syphilis.

An abnormally long cord may become knotted, and so obstructed; or it may wind around the fœtus compressing or grooving the body or limbs, the compression being associated with the atrophy consequent upon obstructed blood flow; an abnormally short cord may interfere with labor; and, finally, the amnion may be fused to the fœtus, giving rise to bands and so interfering with the growth of some part, or by obstructing veins or lymphatics may even cause a localized giant growth.

The Causes of Pathological States Acquired During Parturition.— The causes of these are mechanical, traumatic or infectious. Mechanical causes are either shortness of the cord, preventing descent or producing strangulation, or undue narrowness of the pelvic channel causing prolonged labor and the results that arise therefrom. Traumatic causes are the manual or instrumental aids that may be necessary to complete the process of parturition; such also is the pressure that produces hematoma of the scalp; such the accidents that bring about fractures or dislocations of bones, or birth palsies or hydrocephalus. The chief infectious cause is the presence of pathogenic organisms in the genital tract, especially the gonococcus, leading to ophthalmia. Finally, improper treatment of the umbilical cord may lead to hemorrhage, local suppuration, or to general bacteriemia.

Monstrosities and Abnormalities.—Here in connection with antenatal disturbances we should properly discuss the subject of monstrosities and abnormalities, for these as being away from the normal are pathological conditions. Yet it must be admitted that, with rare exceptions, they are outside the domain of "practical politics." Occasionally, that is, we may remove a supernumerary digit, still more rarely separate "Siamese twins" or remove a teratoid growth, but even then our surgery is largely independent of any knowledge of causation and classification of the conditions. On this account we have relegated a rapid review of the subject to an appendix (p. 813).

POST-NATAL ACQUIREMENT OF DISEASE

Classification of Causes.—The causes of disease acquired after birth are necessarily external. The environment may be altered so as to cause disease, or injurious substances, living or dead, may be introduced into the system. The agents which thus produce disease are:

1. **Mechanical**—inducing "trauma."
2. **Physical**—under which can be included:

(a) Alterations in the pressure of the atmosphere, including both diminution and increase.

(b) Alterations in temperature, local and general, including both heightened and lowered temperature.

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(*c*) Effects of electricity, both atmospheric and induced.

(*d*) Effects of light and of other forms of radiant energy.

(*e*) Effects of soil and climate.

(*f*) Sociological effects, habitation, clothing, dwelling, occupation, and other environmental conditions.

3. **Chemical Causes**—under which, besides (*a*) the gross effects of caustic and other agents upon the tissues, we should include (*b*) the main effects of vitiation of the atmosphere by various gases, and (*c*) the main deleterious effects of improper food and defective nutrition, as again, to some extent, the deleterious effects of certain occupations.

4. **Parasitic**—under which heading are to be included the deleterious effects of:

(*a*) Minute "protista" and vegetable parasites—bacteria and fungi.

(*b*) Minute animal parasites—sporozoa, amœbæ, etc.

(*c*) The larger animal parasites, including worms (cestodes, trematodes, nematodes) and arthropods (arachnids and insects).

As one reads the foregoing table, he will be conscious that many of the agents mentioned are things not in themselves hurtful; some are even therapeutic agents of definite value; it depends upon the degree with which a physical or chemical agent affects the tissues, whether the result will be physiological or pathological.

Mechanical Causes of Disease.—Mechanical causes of disease are:

1. Concussion.

2. Puncture, with which may be included the effects of projectiles under high velocity.

3. Section.

4. Contusion, with which may be included lacerations and tearing.

5. Compression.

6. Distension.

7. Atmospheric pressure.

1. **Concussion.**—This is the effect produced upon a soft, fluid or semifluid body by the momentary application of force; familiar examples are blows upon the brain, or upon hollow viscera with gaseous or fluid contents, such as the lung, the bladder, or the stomach. The brain is a soft substance lying in a bath of fluid; if a blow of sufficient force be struck upon the skull, without fracturing it, the brain may be damaged by being propelled against the opposite side of the skull, inasmuch as, being denser than the fluid in which it lies, it takes more momentum from the applied blow than does the surrounding medium. The small hemorrhages that appear in the brain are not necessarily the result of a direct blow, but of the shaking-asunder action applied by the brain being suddenly brought up against an unyielding surface. A similar result is seen in the case of soft tissues bordering upon a cavity containing fluid or air; a blow may be struck upon the thorax, and imparted to the lung; the part of the lung nearest is set in motion away from the blow, and the air within not being set in motion with as much velocity, the conflict of two degrees of force acting upon the tissue

tears it. Thus is to be explained the rupture of a full viscus such as the urinary or gall-bladder or the intestine. Inseparable from the conception of concussion is the idea of molecular, if not visible, change in the tissues affected.

2. **Puncture.**—A stab wound is a familiar example. The damage may be wrought in various ways; there is a certain destruction of tissue in the path of the blade; there may be great damage done by the weapon piercing a large artery or an important nerve trunk; bacteria may be introduced into the tissues by the instrument, or from a hollow viscus opened up, or along the track of the blade from the air. The puncture of tissues by projectiles is to be considered here; generally speaking, the higher the velocity the more a bullet wound approximates to a "puncture"; with low velocity the character of the wound is more of the nature of a contusion. It will be obvious to the reader that in discussing these mechanical causes, one can rarely adduce examples that are purely of one character; with a punctured wound there may be contusion, and nearby tissues may be compressed against other more solid tissues; and with projectile wounds there will often be concussion.

3. **Section.**—This consists in the cutting asunder of tissues by an edged instrument, and as it occurs surgically, entails a minimum of effect upon tissues other than those cells actually injured.

4. **Contusion.**—Differing from the condition of concussion, we have here the effect of force applied directly to the tissue concerned, forcing cells asunder from cells. The disintegration may be slight, as in contusion, where, it is to be noted, the resulting hemorrhage is mainly responsible for the visible signs; or more severe, as in laceration, or separation of one part from the rest may be brought about. In this form of lesion, also, the injury may afford opportunity for the introduction of bacteria from without or from within.

5. **Compression.**—Compression tends to affect rather the fluid part of the tissues than the solid, and we thus search for its effects in changes in the nutrition of the part; compression made by the weight of the body when blood force is low may so empty the capillaries that the tissues are ill-nourished, and a **bedsore** is produced. In the part beyond a tight bandage, the stagnation of the body fluids may induce necrosis, and the tissues actually compressed are even more liable to suffer. The effect of the gradual pressure exerted by tumors upon neighboring organs causing poor nutrition and necrosis in them is well known.

6. **Distension.**—The principle here is the same as in the last case; a familiar example is the destruction of renal tissue in **hydronephrosis,** where the increasing urine acts as the distending force, until the kidney becomes a large thin-walled cyst.

7. **Atmospheric Pressure.**—Differences in the tension of gases in atmospheric air bring about changes in the tension of gases in the blood and the tissues. If the atmosphere be much rarefied, the amount of oxygen taken up is so reduced that asphyxia supervenes. Where

the atmospheric pressure is greatly increased, as in caissons, there is a greatly increased amount of air taken up. As in a soda-water bottle the greater the atmospheric pressure to which a fluid is subjected the greater the amount of gas that can become dissolved in it. Remove the cork and so remove the pressure and the excess gas becomes liberated. This increased absorption at the moment does no special harm, but when the subject passes rapidly from compressed air to ordinary atmospheric pressure, much of the nitrogen so taken up is suddenly liberated in the form of discrete bubbles which may mechanically interfere with the circulation in the capillaries. The oxygen of the air, it may be added, has become fixed in the tissues. It deserves note that diminished supply of oxygen, whether by exposure to high altitude, or by partial replacement by carbon monoxide, leads rapidly to an increased production of erythrocytes and a condition of **polycythemia** at high altitudes. There is also an increase in the circulatory lymphocytes and blood platelets (Webb).

Physical Causes of Disease.—**Temperature.**—By reason of a very responsive heat-regulating apparatus, the human body can stand exposure to great extremes of temperature, from 100° F. below freezing point to 50° F. above the boiling point of water. Protoplasm will freeze at the one, and coagulate at the other; but the body is protected in the case of cold by a layer of warmed air, and in the case of heat by a layer of air cooled by the evaporation of moisture given off on the surface. If the air be so moist that this evaporation cannot occur, the high temperature at once becomes effective upon the body cells and, therefore, dangerous. The dangerous effects of heat and cold are manifested in local change, which may be called primary, and in certain subsidiary changes affecting the whole system which are secondary. These secondary changes are remarkably similar in the case of heat and cold. Following the initial paralysis of the vessels of the part which are the heat-regulating mechanism, the vitality of the cells is arrested, and they may die, or at the best may throw into the circulation deleterious materials; in addition the sensory nerves of the part are profoundly irritated.

It is thus evident that while heat or cold may cause death, yet short of this the effects are primary and secondary; while the disease-causing agent operates the primary effects are produced, and after it ceases to operate, we have yet to reckon with a train of secondary effects. Here exists the difference between physical and parasitic causes of disease; in the latter we have the continued effect of a constantly present agent, while in the former, we have to meet the after-effects of a temporarily applied disease-causing agent.

Light and Radiant Energy.—The most definite evidence that radiant energy can cause disease is connected with cases where the tissues are affected by the x-rays and radium emanations. It has been estimated that if an ounce of radium could be collected in one mass, merely to pass within a certain distance of it would cause death, and this, of

course, without there being any sensation of heat. Such action we do not yet understand beyond recognizing the existence of rays of different order—α-, β-, and γ-rays—of which the alpha and beta-rays are "soft" and of little penetrative power, whereas the gamma rays are "hard" and most effective in cell destruction, arresting the activity in particular of vegetative cells, such as the germ cells, the cells of lymph nodes and of malignant tumors. These γ-rays, however, are produced in very small quantities. With radium, for example, for them to be produced in affective amounts it is found that as much radium (or mesothorium) must be employed as possible, at close quarters over periods of several hours, the tissues at the same time being shielded from the irritative, more local action of the α- and β-rays either by metal or rubber shields which these latter rays do not penetrate. Where sunlight appears to cause conjunctivitis and inflammation of the skin, it is combined with ultraviolet and other spectral rays, and these last are perhaps the more potent agent of the two. In **sunstroke**, these along with radiant heat, are beyond question the active cause; in **heatstroke**, the rays are not a factor, but this is due to accumulation of body heat in conditions where proper loss of heat from the body is prevented.

The absence of light does not seem to be an active factor in the causation of disease, although its combination with certain frequent accompanying conditions, such as impure air, does in time produce deleterious effects upon the human system.

Electricity.—It is as yet difficult to give much definite information about the effect of electricity upon the tissues. The effects of the constant current are different from those of the alternating; it seems that the former produces less nervous and muscular excitation than the latter. The constant current of considerable strength can produce decomposition of the tissues in the neighborhood of the negative pole, apparently just as it produces electrolysis of water and other fluids. Alternating currents of high potential, the ordinary "live" wire of commerce, appear to cause death by inhibition of respiration. It is a necessary thing for every house physician to know that in case of accident from electricity the worst thing that can happen to the patient is that he should be carried off to a hospital. *Artificial respiration should be begun at once and persisted in;* the loss of time involved in moving the patient may be fatal. It is to be remembered that alternating currents of extremely high rapidity and very high potential can be passed through the human body without injury, although less rapidly alternating currents cause death.

Chemical Causes.—Under this heading are included all those causes in which a direct molecular interaction occurs between the noxa and the cells of the organism.

This interaction may be of the nature of a gross effect, as in the action of a caustic, or of a more indirect effect by which the cells, although not destroyed, have their functions disturbed. Any solid, liquid or gas which is capable of being incorporated with the body

fluids, and thereby coming to act deleteriously upon the cell substance, may give rise to morbid changes, and thus be a poison.

Poisons.—We have just stated that chemical substances that act deleteriously may do so, either as caustics, that is, as substances that injure and kill cells by direct contact with them, or as intoxicants, that is, as substances that act harmfully upon cells by reason of being incorporated with body fluids and exerting their influence upon cells anywhere in the body, even at a distance from the point of first contact. **Intoxication** is the process by which such indirect action is brought about. The term **poison** is so wide, that it includes not only substances that we consider noxious in their very nature, but also substances in themselves harmless which by reason of their amount can interfere with the orderly and proper performance of the duties of the cell. A poison is not only that which induces molecular disturbance and disorderly chemical change in the cell, but also that which interferes with or inhibits the normal molecular changes in the protoplasm. An example of this poisonous action, by a substance in itself no poison, is found in the case of water, which is essential to existence, and constitutes 70 per cent. of the body weight; if it be introduced into the tissues above a certain amount (60 c.c. per kilo of body weight) it may kill. This will indicate how wide a meaning we bestow upon the term *poison*.

Poisons may be at once divided into two groups, **exogenous**, arising outside the system, and **endogenous**, arising within. In defining what is exogenous and what is endogenous, we must be careful; food material in the alimentary canal has not yet become a part of the organism, and is as yet external to the lining epithelium of the body; yet many wrongly speak of the absorption of decomposition products of it as *auto-intoxication*,[1] as if such poisons were endogenous instead of being, as they are, exogenous. The strict and useful definition of the two terms must be held to be: endogenous poisons are substances actually derived from the cells; exogenous those set up by substances foreign to the cells. This latter will include even the products of bacteria in the tissues.

The intoxications then may be grouped as follows:

I. Exogenous Intoxications.

1. *Non-parasitic.*—Intoxications due to the actions of poisons not produced in association with the organism, which gain an entrance into the system through the skin, digestive, respiratory, or urinary tracts.

2. *Parasitic.*—(a) *Parasitic proper*, due to the introduction into, and growth *within* the tissues of parasites of various orders, animal and vegetable, which, growing, give rise to toxic substances.

(b) *Saprophytic*, due to the growth of parasites of various orders on one or other surface communicating with the exterior of the organism, the products of growth becoming absorbed and diffused into the tissues.

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[1] αὐτός, self.

II. Endogenous Intoxications.—Of pure type; auto-intoxications proper.

1. *Internal secretory*, intoxications due to altered internal secretions on the part of the body cells affecting (*a*) the secretory cells and tissues themselves, and (*b*) the other tissues of the organism, through diffusion of the altered products of cell activity.

2. *Disintegrative*, due to the absorption of the products of disintegration of dead cells (*e. g.*, in burns, internal hemorrhages, etc.).

3. *Metabolic*, the results of impaired metabolism and imperfect excretion.

III. Intoxications of Defect.—Under this heading must be included a remarkable series of morbid states, due to defective nutrition, to the absence of an essential food constituent, the relationship of which has been recognized within the last few years. We refer to scurvy, infantile scurvy (Barlow's disease), beriberi, and ship beriberi.

EXOGENOUS INTOXICATIONS—NON-PARASITIC

Foreign substances entering the body or absorbed by it act (1) locally, at the point of application, and (2) in a general way. Wherever sufficient time elapses, there is a local change, degenerative or necrotic; this may be followed by inflammatory reaction. If a poison like hydrocyanic acid be taken in sufficient amount, the general effects are produced so quickly that the local effects have no time to assert themselves.

Poisons may bring about their general effects in the following ways:

1. By arrest of cell activity.

2. By increase of cell activity, followed by exhaustion and paralysis of function.

3. By increase of cell activity, followed by disintegration.

To classify the poisons under such groups would be merely to catalogue them; it is better to realize that toxic agents have selective effects upon different tissues, and in connection with each order of tissue to attempt to arrange the poisons with some reference to the modes of action stated above.

Poisons Acting upon the Nervous System.—The nervous system, on account of its delicate organization, is liable to be relatively often affected by poisons, and we find, therefore, great differences according to the intensity of the dose. By reason, too, of the high degree of development of the nervous system in man, we find that animal experimentation often fails to give us correct analogies, for severe cerebral disturbance (delirium) may be created in man by substances that have little or no effect on lower animals.

Poisons acting upon the nervous system may be grouped as follows:

1. Those causing arrest of cell activity: (*a*) Immediate, *e. g.*, hydrocyanic acid; (*b*) not immediate, *e. g.*, hypnotics and sedatives.

2. Those causing increase of cell activity followed by diminution of function, e. g., alcohol, aldehydes, atropine, etc.

3. Those causing increase of activity, followed by exhaustion and at times disintegration; e. g., strychnine, tetanus and rabies toxins.

It is notable, also, that many of these poisons select particular parts of the nervous system as the sites of their greatest activity. Areas so selected are:

1. *Higher cerebral centres:* Hypnotics, carbon dioxide.

2. *The medulla:* Picrotoxin, apomorphine.

3. *The spinal cord:* Strychnine, brucine, quinine, thebaine, salts of potassium and ammonium.

4. *Peripheral nerves:* Ether, chloroform, carbon dioxide (altering electromobility), diphtheria toxin, and, possibly, lead and alcohol.

5. *Nerve terminations:* Curare, cocaine, veratrine, nicotine.

Confronted by the question how this selective action is brought about, we may say that it is suggestive that the hypnotics, as a group, are soluble in fats and lipoid substances, and the abundance of cerebrosides, cephalins, etc. (which are lipoids) in the nervous system, seems to account for the amount taken up by this particular class of tissue.

Poisons Acting on the Muscular System.—Apart from the effects produced upon striated muscle by the mediation of the nerves, there yet remain some poisons which appear to act directly upon the muscle cell; these either excite increased contractility or make the contraction more feeble. Of the former, the **irritative** examples are quinine, caffeine, veratrine (small doses), hypoxanthine, and creatine, as well as the toxins of the Bacillus coli. Of **inhibitive** poisons may be mentioned the potassium salts, the alkaline earths, and copper.

It is supposed, too, that certain poisons produce definite effects upon unstriated muscle, and it is with this idea that atropine is administered to excite peristalsis in cases of so-called "paralytic distension of the intestines" occurring in peritonitis; morphine appears to arrest peristalsis by a direct action, while ergot and ergamin (β-iminazolylethylamin) are found to stimulate unstriped muscle to contract. Adrenin and barium chloride cause the muscle of the arterioles to contract, although there is evidence that the former influences also the terminal vasomotor apparatus.

Poisons Acting upon the Blood Corpuscles.—The blood corpuscles are protected from many injurious substances by the alteration that such substances undergo in the process of being absorbed; but if injected directly into the blood stream these are effective.

1. **Hemolytics** (Hemoclastics).—The destruction of many blood corpuscles may be brought about by physical means, such as altering the tonicity of the plasma by the injection of water, or by freezing or by thawing. Some drugs, such as saponin, abrin, and ricin are effective, and many bacterial toxins and animal venoms. Also dangerous to the body, though without there necessarily being hemolysis, are those stable combinations of hemoglobin with carbon monoxide, carbon

dioxide, cyanogen, and the cyanates which prevent the proper absorption of oxygen and carbon dioxide in the normal process of respiration, and so cause asphyxia.

2. **Leukolytics.**—There are some poisons which can cause destruction of white blood corpuscles, but one must be careful to note that leukopenia (lessened number of leukoeytes in the circulating blood) may not be due to destruction of leukocytes so much as to altered distribution in the body at large. Pancreatin can, however, cause their destruction, as also can the presence of bile salts in excess. Where the destruction can be recognized, it is quickly followed by the appearance of a leukocytosis, which is, again, at first not so much due to regeneration as to redistribution.

Poisons Acting on the Organs of Circulation.—Poisons may affect (1) the heart, or (2) the vessels, particularly the arterioles, or (3) the nerve centres that control the cardiac mechanism; it is extremely difficult for the observer to know which of these is being acted upon the most, because their relationship in function is so intimate.

Poisons Acting upon the Heart.—It has been determined, however, that certain substances such as digitalin, digitalein, digitoxin, strophanthin, and the barium salts cause stoppage of the heart in systole, whereas arsenic, antimony, potash, chloroform, and alcohol in sufficient doses can cause stoppage in diastole—which last is perhaps the reason for the occurrence of acute dilatation of the heart in drunkards. The heart whose ventricle stops in diastole fails not because of inhibition, but because of paralysis of the accelerator nervous mechanism.

Poisons Acting upon the Vessels.—These cause (1) contraction or (2) dilatation, by direct action. Ergot and ergotin cause contraction of the arterioles by direct action, apart from their influence upon the heart. Adrenin and barium chloride do the same. Dilatation, on the other hand, is directly produced by the nitrites, chloral, quinine, and atropine (small doses). It is a strange fact that some of the drugs mentioned have a selective power upon the vessels of certain organs. Quinine acts especially upon the spleen, digitalein upon the kidneys, amyl nitrite upon the superficial facial vessels and upon the respiratory tract. Adrenin, while it causes the vessels of most organs to contract, when applied to the surface of the pancreas causes vasodilation.

Poisons Acting upon the Digestive System.—It is necessary when examining the effect of a poison upon the digestive tract to ascertain its effect when introduced into the digestive channel, (a) with the vagi and sympathetics intact, and (b) with the same divided, and also, when introduced subcutaneously. It will be seen that, by reason of the intricacy of the mechanism, the possibilities of error are great. Apomorphine, to induce emesis, must be injected subcutaneously, ipecacuanha must be put into the stomach with the vagi intact. If the vagi are cut, even large doses are ineffective. Magnesium sulphate introduced into the blood or subcutaneously will cause only moderately increased peristalsis; introduced into the bowel it causes abundant, watery evacuations.

Poisons Acting in the Mouth.—All the poisons which cause increase or diminution of salivary secretion require first to be absorbed, and their action is thus reflex.

Poisons Acting upon the Stomach.—Vomiting is a process in which the nervous system is dominant, whether the impulses be originated from the medulla or from the nerve endings in the stomach. There are many irritant poisons which can set up irregular peristalsis, contraction, and relaxation of the stomach walls.

Poisons Acting upon the Intestine.—Diarrhœa is to be recognized as a term which may refer to two distinct processes. These are: (1) the premature discharge of the contents of the small intestine without due absorption and modification, and (2) the discharge of excessive secretion from the mucosa of the intestine. The first of these is due to increased peristalsis. Croton oil produces this directly; rhubarb or senna injected into the veins will cause it, and aloes when injected, only when there is a free flow of bile. The second process, the increase of secretion, is produced by the saline purgatives and by sundry bacteria, such as cholera vibrio.

Actual lesions of the intestinal wall are produced by poisons in two ways: (1) by direct effect, and (2) in the process of being eliminated into the bowel after being absorbed there or elsewhere. The former are most likely to be situated in the upper part of the tract, and, in the case of caustics, at narrow places. The latter, the eliminative lesions, may occur in any part of the tube where the secretory structures are numerous. Duodenal ulcers, as they are observed in burns, may be of this nature; the so-called uremic ulcers undoubtedly are. Ulcerations and other lesions seen in the colon after the ingestion of corrosive sublimate may be reproduced if the poison be introduced by other paths, and thus are definitely due to elimination.

Poisons Acting upon the Liver.—One of the most important, if not the most important, of the functions of the liver is to stand between bodies of a poisonous nature absorbed from the alimentary tract and the body. By its site at the head of the portal system it comes in contact with, neutralizes or eliminates these bodies brought by the portal blood. This it does sometimes at a heavy cost to itself. Nor is it only with portal blood that it has to deal, for sulphindigotate of sodium introduced into the circulation entered the bile one minute later, and must have passed to the liver directly by the arterial supply. The various poisons with which the liver has specially to deal and which are prone to cause damage to it, may be grouped as follows:

1. Metals and metallic salts, phosphorus, arsenic, lead, mercury, and copper. After ingestion, upon analysis, these substances will be found in greater quantity in the liver than elsewhere; and as they are excreted in the bile they are in part again absorbed by the bowel, and carried once more to the liver.

2. The toxic products of digestion, indol, skatol, phenol, the poisonous diamins, kyrins, are due either to the action of the digestive juices or,

perhaps more frequently, to the fermentative activities of the intestinal bacteria upon the foodstuffs. When these are in excess, the liver cells cannot handle them, and the overplus goes into general circulation, to the detriment of the body.

3. The toxins of pathogenic bacteria. It is one of the most frequent of observations that the liver suffers in acute infections, either showing cloudy or more severe degeneration, or even actual cell death (focal or general necrosis).

4. The products of destruction of the red-blood cells (hemolysis). It has been found that as a consequence of certain toxemias the liver becomes incapable of dealing with the excess of blood pigment given to it; and although the original toxemia may be partly to blame, the excess of pigment itself appears to take a part in causing the damage.

Poisons Acting upon the Kidneys.—The general statement just made, that the organ whose duty it is to handle toxins must itself suffer, applies to the kidneys as it does to the liver; the kidneys must bear the brunt of the toxic substances in the systemic circulation; certain of the metals mentioned in the case of the liver are equally effective upon the kidneys; while certain other substances, such as cantharidin and uranium nitrate and the toxin of scarlet fever evince a distinct predilection for these organs.

EXOGENOUS INTOXICATIONS—PARASITIC CAUSES

The parasitic causes of disease are: (1) microparasites of vegetable nature; (2) microparasites of animal nature, and (3) larger animal parasites. Some of the intoxications so caused are from toxins manufactured outside the body, as, for example, where the parasite infests the alimentary tract (strictly *outside* the body tissues), as happens with the ectotoxins of the *B. botulinus* in certain cases of meat poisoning. By far the most, however, are intoxications caused by parasites living within the tissues.

The Normal Defences of the Organism.—It is necessary to consider the ways in which bacteria gain entrance to the tissues, and the means possessed by the body of defending itself against them. The human body has a continuous external covering, one purpose of which is to prevent the entrance of organisms; this means not only the skin, but also the lining of every cavity or space that opens directly or indirectly upon the surface. The only break in this continuity of covering in the human body is in the case of the opening of the Fallopian tube to the peritoneum; this has so fine a channel and is so deeply situated, that it is, to all intents and purposes, closed. Yet this opening has proved, even in apparent health, the port of entry for organisms, peritonitis being set up. With this single exception, the human body is a "close corporation." On the outside, on the skin, in the mouth, in the upper air passages, in the intestines, in the female genital tract,

are countless billions of bacteria. Do these never succeed in getting past the barriers? A small proportion of them do so constantly, but there are many mechanisms waiting to deal with them, and in health their tenure of existence within is a very short one.

The mechanisms referred to are these:

1. **Surface Washing.**—The bacteria on the skin are being constantly removed by washing or by friction, and those in the mouth are washed down by the saliva to the stomach, where the acid gastric juice kills the majority of them. The mucus in the mouth, the respiratory tract, the alimentary tract, and the female genital tract, while it catches bacteria as a flypaper catches flies, offers a physical barrier to their contact with the surface cells, and is itself by gravity or by peristaltic movement or by ciliated epithelium apt to be carried away. It is considered by some that mucus, itself, has bactericidal power.

2. **Gastric Juice.**—The action of the gastric juice has been mentioned. The food contains countless bacteria; yet the duodenal contents at times are almost, if not quite, sterile. It is a common observation that most peritoneal infections from perforation of the stomach or the upper part of the intestine are less virulent than from perforation of the ileum or colon, which is doubtless due to the killing of many and the attenuation of other bacteria in the stomach. With diminution or absence of the hydrochloric acid in the gastric juice this no longer is true, because the bacteria unkilled in the stomach pass down living to the more alkaline, and, therefore, more suitable medium in the lower bowel, where their multiplication may do damage. It is to be noted that the musculature of the stomach is so arranged that fluid, such as water, taken between meals, *i. e.*, without solid food, may pass without arrest along the lesser curvature into the duodenum. In this way the contained bacteria may escape destruction. In the feces, of course, enormous numbers of bacteria are removed from the body. As an indication of the extent of bacterial growth in the intestines it may be said that on an average 25 per cent. of the dried feces has been found by competent observers to be composed of bacterial bodies, the vast majority dead—killed it would seem in the progressive concentration of the intestinal contents which takes place in the colon. According to Mattill and Hawke the average daily amount of *dry* bacteria discharged *per anum* is 8.27 grams, or otherwise, over 2 drachms.

3. **Physical Hindrance in the Respiratory Tract.**—If air containing dust and other particles impinges upon a moist surface, the solid particles adhere to it; the breath that is drawn through the nose, passing through the devious maze of the turbinate bones and deflected by the pharyngeal surface is very thoroughly purified before it reaches the trachea, and in health the expired air is found free from organisms. It has been pointed out that the varying caliber of the larynx and trachea induces a spiral motion of the inhaled air, thus bringing each successive portion of it in contact with the lining mucosa, so additionally insuring the arrest of solid particles. The particles that lodge on the

surfaces are either expelled again with the nasal mucus in blowing the nose or by expectoration, or they are swallowed, or, in the case of a small percentage of them, absorbed into the tissues that surround the upper respiratory tract. These particles are of many sorts—bacteria, dust, smoke, and so on. Among them there are sure to be many that are a menace to the individual, and it is for the disposal of these, in part, that nature has provided so large a mass of lymph tissue in the neighborhood of the upper respiratory tract. Between the level of the roof of the pharynx and the top of the sternum there are very numerous collections of lymph nodes, varying in importance from the tonsils to the smallest cervical nodes, all together constituting a large amount of tissue. Just as a country places most garrisons near the frontier that is most open to attack, the body has its garrisons of protective lymph nodes around the road by which the invaders are most likely to come—the upper air passages. Particles on the surface are constantly being deported by the mucus and saliva, in which they lie, being carried toward the entrance by the cilia of the epithelium lining the tract.

4. **Protection by Leukocytes.** — On mucous surfaces there are frequently free leukocytes that have wandered from the blood stream between the superficial cells. These engulf particles of dust, bacteria, etc., and wander back with them into the tissues. Apart from the digestant or solvent effects of the cytoplasm of the leukocyte upon its captive, the foreign body is thus imprisoned, and for the time being not capable of doing hurt to the body. No commonwealth fears very greatly criminals or other enemies, if each criminal is handcuffed to a policeman. The leukocytes which wander back to the tissues are carried by the lymph stream to the nearest lymph node where the intruder, if a bacterium, is killed by the leukocyte or if the leukocyte be weakened by its struggle with the bacterium both are engorged by one of the large endothelial cells—the macrophages—which line the lymph sinuses. *Bacteria are, therefore, constantly finding their way into the tissues, but under such circumstances do not cause infection. In health they are destroyed soon after their entry.*

This process is going on constantly in the tissues underlying all the moist surfaces of the body, and in none to a greater extent than in the intestines. It is scarcely credible that the absorption of so many and various substances from the bowel cavity takes place without there being included many bacteria; these have to run a triple gauntlet before they are free to do harm—first, the lymph tissue which is so abundant in the submucosa; second, the mesenteric and retroperitoneal lymph nodes; and third, the liver itself. Finally, bacteria which escape these may become free in the blood, and although we have hitherto said nothing of the bactericidal property which the blood and the body fluids possess, yet these are of the very first importance.

The impression is widespread that the systemic blood is sterile, but this is probably only relatively true. Evidence seems to indicate

that bacteria enter the blood, but are quickly attenuated and killed, whether they exist for this short time free in the fluids or engulfed by leukocytes. The solid internal organs—spleen, kidney, etc.—have been proved to contain bacteria, but appreciable growth from them is slow, presumably because most of the bacteria in a given organ at the moment at which the animal is killed are in an attenuated state, and probably die in the culture medium, while those deposited there at the latest moment before death are the only ones that are viable, and they are in so small number that appreciable growth in the culture medium is delayed for a time. This is the reason why cultures made from such organs, if observed only for two or three days, are reported as sterile, and in any case, appear to grow but sparingly. As an illustration of the protective mechanism of the body, may be quoted the experiment that if large quantities of bacteria, even pathogenic, be injected into the blood stream, a few minutes later only a few colonies can be grown from the circulating blood, and after an hour probably none at all. The endothelium of the blood vessels of all the organs has been active in removing the bacteria, the leukocytes have been engulfing them, and the bactericidal substances of the blood killing them. A few hours later, however, the blood is again teeming with them. This is because some attenuated, half-killed, or uninjured bacteria, tucked away in some corner with insufficiently powerful cells opposed to them, have waited their opportunity, have won their local battle, and multiply, soon flooding the tissues now exhausted of their protective forces. If one uses a homely example, the inroad of the bacteria is like a prairie fire, attacked and beaten out by an army of fire fighters; some spot left smouldering bides its time, and blazes up; the fire fighters exhausted by the previous struggle cannot cope with it, and it sweeps everything before it. It is possible to find in microscopic sections of the liver dots, single, double, or treble, which are the remains of bacteria, and often whole bacteria themselves. Granting all the foregoing evidence, nevertheless, *the healthy tissues are potentially sterile.*

Modes of Infection.—Since there are many ways by which bacteria enter the tissues, it is evident that there are many ways by which infection can arise. Infection implies not the mere presence but the successful multiplication of bacteria in the tissues. The factors that make possible the latter are these:

1. **Traumatic Solution of Continuity of the Surface Layers.**—Here an ingress is provided for the bacteria, and the damaged tissue is a favorable ground for them in which to multiply. This lowered vitality of tissue is most important. The result is familiar to everyone who has seen an infected wound. Let us follow the process in a wound of the skin. Lying deep down in the layers of the skin, and in hair follicles, is the *Micrococcus epidermidis albus*—perhaps an attenuated form of the ordinary staphylococcus, but leading a harmless saprophytic existence. Let a tight suture in a wound lessen the blood supply of the underlying tissue, this organism, so weakly pathogenic that it

cannot ordinarily live *within* the tissues, has power to grow, to increase its virulence, and to break down the tissues already weakened by the trauma of the knife cut. This is the genesis of "stitch abscess." Further, the organism which infects the wound need not be a local inhabitant of the tissues; we have pointed out that there are bacteria of many sorts leading a brief existence in the circulating blood; one of these in the few moments of life that would, under normal circumstances, remain to it, may be carried to the damaged area of the wound, where it finds the tissues in a state, not only not inimical, but even favorable to its growth. Such is the genesis of some wound infections. Everyone who has followed the work of a busy surgeon has seen "aseptic" operative cases become infected, and die; heart burnings and self-accusations, and suspicion of the assistant's fingers, and of the instruments, and of the ligatures have followed, all of which tends to keep an operating staff eternally vigilant. This is a good result following a tragic affair; we would not lessen, for an instant, the mental effect of such cases, but we cannot in justice refrain from indicating the method in which such an accident *may* occur.

2. **Alteration of the Surface Discharges and Secretions.**—When in a fever the salivary secretion is lessened, the mouth becomes foul and bacteria, instead of being swept away, remain *in situ* and multiply; their toxins cause necrosis of the underlying surface epithelium, and an ulcer results, so that there is now provided a suitable medium for growth of the bacteria in the damaged tissue and an entrance into the body. Similarly in the bowel, if an obstruction occur, the bacteria in the contents above the obstruction multiply, give off increased toxic products, and rapidly increase in virulence, an observation that is readily verified by experiment.

3. **Growth of bacteria and infection in an internal organ with no recognizable solution of continuity of the surface—"Cryptogenic infection."**
An osteomyelitis of streptococcic nature, for example, is seen to arise without any surface injury or recognizable trauma, or a joint affected by rheumatic arthritis is aspirated and a coccus is cultivated therefrom. This is clearly a case of cryptogenic infection. Why, then, if bacteria are in the circulating blood, is it not a constant occurrence? There are doubtless several factors which must be concurrent, but one of them is that there must be the requisite quantity of infection. Just as one swallow does not make a summer, one bacterium does not make an infection. An organism, carried into the tissues or the blood stream by a leukocyte, unless it be exceedingly virulent, can hardly set up an infection, because the tissues, if not the leukocyte, are able to overcome it. We suppose that a number of associated circumstances are necessary: (1) the presence of a goodly number of bacteria upon some mucous surface; (2) a congestion with many leukocytes passing out and returning with many bacteria; (3) accumulation of so many bacteria at one spot that the tissue resistance becomes exhausted, and probably (4) lowered vitality of the tissue at this area before the bacteria were

introduced. One need only strike a joint of the rabbit's limb with the side of the hand and then inoculate in the blood a suspension of streptococci to insure that that joint becomes the seat of an acute streptococcal arthritis. Infection is thus the outcome of a contest between the bacteria and the tissues, in which the former win.

How Bacteria Enter the Body.—Pathogenic bacteria have different habits of growth; some require the animal body for their nidus, others the human body, and such, if discharged from the body, do not multiply, although they may for a long time retain their vitality. It is essential for such bacteria that when discharged from one body, they find another in which to grow. They can be carried by direct contact, or by the air, or through the medium of **fomites** (*i. e.*, in garments, in dust, in scales of shed skin), or by the discharges of one person getting into the water, milk, or food taken by another. Insects, too, may carry the bacteria, but they act only in a passive way, that is, the bacteria do not actually undergo any definite cycle of life while in the body of the insect. There was a time when "contagious" diseases meant something essentially different from "infectious" diseases; the distinction is now a useless one, since we know that it was not the "contact" that made a contagious disease contagious, but the infection. **Infectious** is the better term to apply to all these diseases.

The habitat of a bacterium will be of some effect in determining the portal of entry to the body; thus (1) organisms floating in the air are likely to be taken up by the respiratory tract, especially the nose, pharynx, or tonsils. (2) Any bacterium entering the upper respiratory tract may be entangled in saliva or mucus and swallowed. Bacteria which can multiply in water, like the Spirillum choleræ and the Bacillus typhosus, are liable to gain entrance by the intestinal tract in food or drink; similarly, any bacteria which, though not able to proliferate in the water or in milk, yet gain entrance to such supply, and are ingested before they die, may infect by way of the intestinal tract. (3) The organisms which normally inhabit the skin, and others whose presence on the skin is adventitious, may be carried into a wound, or an instrument or weapon may itself carry in bacteria, as occurs, for example, in tetanus following a wound from a dirty, often rusty instrument. Further, (4) bacteria infesting the genital passages may be conveyed to the other sex in sexual intercourse, and (5) infection of the placenta may pass to the fœtus by the umbilical vein. With these various facts it is also necessary to remember (6) that the bacteria may pass the portal of entry and manifest themselves at some point of lowered resistance in an entirely different part of the body. Recent observations have shown that a normal lymph node is not a perfect filter and that within a very few minutes after inoculating bacteria into the tissue of the leg these bacteria may be found in the circulating blood, past the inguinal nodes; if, however, a preliminary inflammation of the lymph nodes be caused, the bacteria are wholly arrested, not appearing in the blood. The inflamed node is then a perfect filter by reason of the complete filling of its sinuses by cells.

Bacteria as Causes of Disease.—With the exception of the "filterable viruses" to be discussed later, bacteria are the most minute forms of life known to us; they seem of uniform consistence, have no nucleus, do not conjugate, but multiply by fission; some are motile, by means of flagella, and some have a resting stage of distinct character—the spore; according to their shape, for purposes of description, they are separated into the spherical or bluntly oval **cocci**, the rod-like **bacilli**, and the spiral or curved-in-more-than-one-plane **spirilla**.

Bacteria grow between widely separated limits of temperature, and in widely diverse media; of pathogenic bacteria in general it may be said that they grow best at a temperature near the body temperature of the host, and in faintly alkaline media containing organic matter. Most bacteria grow best in the presence of free oxygen (**aërobes**); many can exist also in the complete or almost complete absence of free oxygen (**facultative anaërobes**); some can grow only in the absence of free oxygen (**obligatory anaërobes**), obtaining the necessary oxygen by breaking up organic material. Bacteria take their food by absorption, and secrete enzymes, by means of which they can bring about in various substances the changes necessary to render those substances capable of absorption. The enzymes are of different orders in different species, **proteolytic** (protein splitting), **diastatic** (carbohydrate-splitting), **glycolytic** (sugar-splitting), and so on; and the distinctive power possessed by a species may at times be changed, so that bacteria in a proteid medium, which are capable of forming proteolytic ferment, may, by being grown in a carbohydrate medium, in course of time, become capable of forming a diastatic ferment; and forms which are inert toward certain sugars may in course of time become capable of fermenting them. What for our purposes is most important, certain bacteria have toxic properties: into the nature of these we must enter in more detail. According to the presence or absence of such, bacteria are divisible into three groups:

1. The non-toxic.

2. Those ordinarily incapable of multiplying within the tissues, but grown outside the body capable of producing toxins which, if absorbed, are injurious. Here belong many saprophytic and putrefactive bacteria, which may become lodged in wounds and set up irritation there, and may give off for absorption their toxins, without themselves gaining entry to the tissues. Here also belong some of the normal inhabitants of the intestine, which, in excess, may give off toxins that are dangerous to the host if absorbed. Some of these last, at times, are converted into members of the following group:

3. Bacteria capable of growing in the tissues (and giving off toxins) and there setting up **infection**. From the foregoing it will be apparent that a bacterial intoxication is the condition in which the action of the products only of bacterial growth is considered; while an infection is that condition in which, in addition to the intoxication, the bacteria themselves are in the tissues and are multiplying there. The prerequisite of an infection is that the pathogenic agent grows within the tissues.

6

Toxins.—Hitherto it has been usual to recognize two orders, namely, the *ectotoxins* discharged by the growing bacteria, and the *endotoxins* liberated only upon the death and dissolution of the bacteria. Within the last year or two, thanks especially to the labors of Vaughan, of Ann Arbor, strengthened by those of Abderhalden and Friedberger, there has been increasing realization that the mode of action of the two orders of toxins is widely different and a tendency to confine the use of the term toxin to the former. For the time being we shall employ both terms, emphasizing that they indicate in all probability bodies of widely different nature.

Stated briefly, the modern conception of these bodies is as follows:

The observations of Abderhalden and others upon *parenteral diges-tion* indicate that whenever a foreign protein gains entrance into the blood and tissues, as distinct from the alimentary canal (enteral diges-tion), within a few days the body cells elaborate and discharge into the blood a specific enzyme, acting upon this particular protein and breaking it down into proteoses and simpler molecules, a process in every way comparable to that to which the ordinary food proteins are subjected in the digestive tract, but differing to this extent, that the proteoses and possibly other dissociation products of a distinctly toxic nature in their absorption through the intestinal wall undergo, normally, conversion into harmless bodies; whereas in parenteral digestion this conversion may not take place.

When first a foreign protein, such, for example, as the white of egg, is introduced into the tissues it is relatively inert and harmless; at most it may be broken down partially by certain non-specific proteolytic enzymes during the first few hours, and the products absorbed into the cells and irritating them set up a certain amount of fever, but very little beyond this. It requires ten days or so before the cells gain the power, through enzyme action, of active dissociation of this particular protein. Once gained, following the general law to which reference will later be more fully made (p. 157), the specific enzyme is produced in excess and discharged from the cells into the blood and lymph, so that if now a second injection of the foreign protein be made, that is dissociated so rapidly that a sufficient amount of toxic material is liberated at one time to set up an acute intoxication, the condition, in short, of **anaphylatic shock.**

Now on the one hand pathogenic bacteria gaining entrance to the tissues may be regarded as foreign proteins. What is striking is that the majority during their growth discharge little active irritative material. We may grow forms like the typhoid and tubercle bacilli and streptococci outside the body for several days, filter off the bacteria and inject the fluid of growth into animals in relatively large quantities without setting up serious disturbance. Such microbes we are accus-tomed to say produce only endotoxins. The process of events when these gain entry into the body for the first time appears to be this: As totally foreign proteins the body cells and fluids are unable to

digest and act upon them. Some may be taken up by cells and partially acted upon by the ordinary non-specific proteolytic enzyme, but the majority finding suitable foodstuffs in the body fluids grow and multiply actively. This period of growth with little reaction on the part of the tissues constitutes the *incubation period*. Gradually those cells which have taken up the bacteria gain the power of forming a specific enzyme, capable of breaking down rapidly the bacterial proteins and, producing this in excess, discharge it. This acts extracellularly upon other bacteria whose products of dissociation, diffusing out and absorbed by other cells, stimulate them to produce specific enzymes, until eventually so considerable an amount of the enzyme is freed and acts locally upon the invading bacteria that they are digested, broken up, and dissolved. It is in this process of parenteral digestion of the bacteria that the toxic moiety of the proteins is liberated, and it is this toxic moiety that constitutes the *endotoxin*, and gives rise to the specific symptoms of the disease.

Expressed otherwise, the tissues gain the power of *bacteriolysis*, and it is certain of the soluble products of bacteriolysis which, diffusing into the lymph and blood and taken up selectively by one or other order of cells, so disturb the metabolic processes in these cells as to induce the symptoms of disease.

This on the one hand; on the other, it has to be realized that just as certain cells of the body, such as some of those lining the digestive tube, discharge enzymes which break down the more solid foodstuffs, converting them into soluble substances which can be absorbed, so certain bacteria secrete enzymes, proteolytic, glycolytic, cellulose-fermenting, and so on, by which they disintegrate the foodstuffs in their immediate neighborhood and prepare them for absorption and assimilation. The evidence is increasing that the *ectotoxins* are bodies of this nature, that they are enzymes which split up the proteins of the host, and, doing this, split off toxic proteoses. *Thus with the endotoxins it is the split products of the bacteria which cause disease, with the ectotoxins the split products of the body proteins of the host.* In favor of this view are the following facts: (I) Like enzymes, minute quantities of the ectotoxins produce maximal disturbances; (II) the poisonous action is not immediate but cumulative, showing itself after several hours; (III) they are extracted and precipitated by the same bodies which extract and precipitate enzymes. (IV) Both orders of bodies are thermolabile, destroyed by a temperature of 50° to 60° C.; (V) both diffuse slowly. (VI) It has been shown by Abderhalden by optical methods that the ectotoxins have a cleavage effect upon proteins, *i. e.*, that they act as proteolytic enzymes, splitting complex proteins into simpler bodies. (VII) Their presence in the animal body leads to the production of specific neutralizing *antitoxins* in every way comparable with the *antienzymes* by which the body neutralizes foreign enzymes.

Long years ago Sidney Martin called attention to the fact that a

toxic albuminose is to be found in the spleen and other tissues of animals inoculated with diphtheria, whereas it is present in minute amounts only in the diphtheritic membrane, *i. e.*, in the region where the diphtheria bacilli are growing, and from his observations concluded that the bacilli elaborate an enzyme which, diffusing slowly into the tissues, thereby its action produces the true toxic substance. The evidence, therefore, is that the ectotoxins are not themselves poisonous substances or toxins, but are *toxases* or *toxogens*, giving origin to toxins.

It is to be noted that relatively few pathogenic bacteria produce ectotoxins in appreciable quantities: B. diphtheriæ, B. tetani, B. botulinus (meat poisoning), and B. pyocyaneus.

The Virulence of Bacteria.—The virulence of a bacterium is measured by the amount and the quality of the toxic substances it liberates either in its growth or in its disintegration. From what has been said previously, it will be inferred that virulence depends upon three variable factors—the quality and the amount of toxins, using this term to include both ectotoxins and endotoxins, and the number of bacteria.

The quality of toxin is specific in a two-fold sense: different species of bacteria produce different toxins, and toxins are active upon some species of animals and not upon others. Regarding the first of these statements, it is true that bacteria of allied species produce multiple toxins, some of which are common to all the members of that group of allied species; yet others are specific for each member of the group. With reference to the second statement, it is necessary only to mention the gonococcus which is active for man but not for the lower animals, and members of the group of the hemorrhagic septicemias of various mammals and birds which are without effect upon man.

Nor are these the only variations. If the same organism be isolated from two individuals, the virulence of the one strain is never, or hardly ever, experimentally identical with the virulence of the other. Further, alterations of virulence can readily be produced experimentally by "passage" through the bodies of animals susceptible to the bacterium concerned. If inoculation of a pathogenic dose be performed, and if as soon as symptoms of disease present themselves, the body fluids containing the bacteria be inoculated into a second animal, and so on, the virulence can be heightened by a few transmissions, so that a much smaller dose will cause disease in a much shorter time than was at first the case. It has been occasionally noted that this procedure, while increasing the virulence for the species concerned, lessens the virulence for certain other species.

In a manner contrary to the above, there are certain methods at our disposal by which the virulence of a bacterium can be lessened. Thus, by prolonged growth upon media, with transference at long intervals, the virulence of all pathogenic bacteria is lessened; bacteria "stewing in their own juice" rapidly lose virulence. Certain other procedures effect the same end, such as prolonged growth at a tempera-

ture near the maximum at which vitality can be preserved, exposure to sunlight, exposure to small quantities of antiseptic substances and increased atmospheric pressure. It may be broadly stated, that for bacteria as for men, within certain limits, the struggle for existence improves the breed; if circumstances be made too easy the breed ceases to advance; if too difficult, it becomes enfeebled.

Other Pathogenic Vegetable Forms.—Biologically higher in the scale than the bacteria or schizomycetes, but of lesser pathogenic importance are sundry "**hyphomycetes,**" and **blastomycetes**, simple forms of vegetable life characterized, the former group by the development of long-branching filaments or *hyphæ*, the latter by the presence of rounded or oval elements much larger than cocci, multiplying by budding as well as by sporulation. These forms are closely connected; thus the organism of blastomycetic dermatitis, a skin affection which was first observed in North America, when within the tissues, exhibits only the rounded, budding form, although when grown in media outside the body it develops distinct hyphæ. Intermediate between these and the bacteria proper are the so-called **streptothricæ**, forms much more minute than the ordinary hyphomycetes, of which the ray fungus or actinomyces may be taken as type. These are forms which, while having the same diameter as the ordinary bacilli, unlike those bacilli, exhibit true branching and tend under favorable conditions to form a mycelium or felted mass. These, indeed, are very closely related to the tubercle bacilli and "higher bacteria" which also under favorable conditions may exhibit true branching. The more highly differentiated are these forms, the less frequently are they found as causes of disease. The moulds, for example, have rarely more than a superficial development, and that upon the skin or in the passages communicating with the exterior, especially the respiratory tract, and with rare exceptions their growth is purely local, setting up little general reaction, and exhibiting little or no power to form toxins. Among these may be mentioned the organisms of ringworm, favus, pityriasis, thrush, and aspergillosis.

"Yeasts" or blastomycetes may be found multiplying within the stomach and urinary bladder, there showing no tendency to invade the tissues. It is only in connection with the skin and subcutaneous tissues that these set up a low intractable form of inflammation, though eventually the organism of blastomycetic dermatitis may grow in all the tissues of the body. The most serious local and generalized lesions are set up by members of the intermediate group (the streptothricæ) which cause lesions of a tubercular nature resembling in many respects those induced by the tubercle bacillus.

Filterable Viruses.—There is a group of important infections which in their clinical course resemble those induced by pathogenic bacteria, but for which, despite abundant investigation, no bacteria proper have hitherto been isolated: we refer to the group of acute exanthemata—smallpox (and vaccinia), chicken-pox, scarlet fever, measles, rötheln; to rabies, acute anterior poliomyelitis, and yellow fever in

man, and among lower animals, horse-pox, sheep-pox, contagious pleuro-pneumonia of cattle, and several other infections. With these are to be included a group of evidently contagious epidermal disturbances—trachoma, molluscum contagiosum, verruca vulgaris (the common wart), verruca peruviana in man, and other "epithelioses" in birds and other animals.

The first light thrown upon this group was the determination by Nocard and Roux more than twenty years ago that contagious pleuro-pneumonia of cattle is due to an ultramicroscopic organism, or, more accurately, to an organism just visible in cultures, but so small that the highest power of the microscope gave no satisfactory indication as to its morphology. They were able to cultivate this, recognizing the growth by a clouding of the medium; others since, employing special media, have gained more visible growths of minute polymorphous forms unlike bacteria, but more nearly resembling those than any known form of life.

Fig. 16

1   2   3
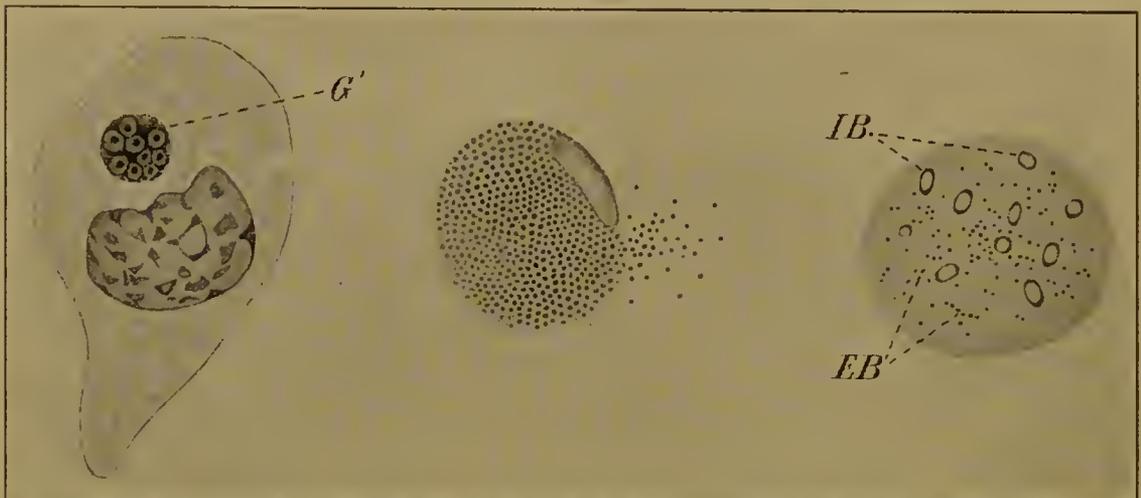
Chlamydozoa, to show various stages according to Prowazek and da Rocha-Lima.   1, a cell from the corneal epithelium after inoculation with vaccinia lymph.   The bodies in the centre of each granule of the "Guarnieri body" (*G'*) are more of the nature of "initial" than of "elementary bodies;" 2, epithelial cell from case of molluscum contagiosum treated with water so as to swell and rupture the cell, liberating the minute "elementary bodies;" 3, conjunctival cell from case of trachoma showing (*IB*) the larger "initial bodies"[1] and (*EB*) the minute "elementary bodies." (After da Rocha-Lima.)

Gradually it has been demonstrated that in one after another of these diseases we deal with a virus so small that it will pass through a moderately fine biscuit porcelain filter, a filter which arrests all bacteria proper: the filtrate from the infective material inoculated into susceptible animals will reproduce the disease. Clearly, therefore, *whatever the nature of the virus, in one stage of its existence it is so minute as to be filterable.* That the virus is particulate is shown by the fact that employment of colloidal membranes gives a harmless filtrate.

[1] It is deserving of note that Wolbach and McKee are inclined to regard these initial bodies as degenerated bacteria, *e. g.*, gonococci.

We thus recognize today that variola, measles, rabies, yellow fever, acute poliomyelitis, and, in fact, practically all the conditions above enumerated are due to filterable viruses, and as with the pleuro-pneumonia organism, some at least, such as those of acute poliomyelitis (Flexner and Noguchi) and rabies (Noguchi), have been gained in pure culture.

Now, in rabies (Negri bodies), molluscum contagiosum, smallpox (Guarnieri bodies), trachoma, and several other conditions, cell-inclusions have been described by several observers, bodies so large as to be easily recognizable and, indeed, used for diagnostic purposes. On this account von Prowazek describes these organisms as *Chlamy-dozoa*. The organisms themselves he regards as ultramicroscopic, and as gaining an entrance into particular cells, sometimes, indeed, into their nuclei. But, gaining entrance, some at least set up such a reaction that the cell forms a coat or garment[1] around them, and it is this cellular deposit with the minute organism or a group of organisms in the centre that indicates the existence of the disease. He and his fellow-workers distinguish two stages, namely, the very minute "elementary corpuscles" and larger "initial bodies" from which the former are discharged.

FIG. 17

Spirochetes in liver of congenital syphilis (oil immersion): *a*, spirochete; *b*, nucleus of degenerated liver cell.

Spirochetes and Treponemas.—Great interest has centred of late upon the spirochetal organisms causing European and African relapsing fever, certain diseases of geese and other birds (spirillosis), frambœsia (or yaws), and syphilis. These organisms are minute, elongated spiral bodies, differing radically from the spirillaceæ, more particularly in

[1] Χλαμύς (chlamys) a mantle.

that their bodies are not rigid, and in the absence of terminal flagella. They are actively motile with a corkscrew-like motion. There is still some uncertainty as to their mode of division, there being positive observations that this is longitudinal, but this does not wholly exclude the observation by other equally competent observers, that transverse division obtains. There is also evidence that in many of them another process of multiplication occurs, the spirochete breaking up into a number of granular, spore-like bodies, so small as to be filterable, from each of which a new organism develops. Their behavior toward salvarsan is so similar to that of the trypanosomes to other arsenic compounds, to that of the piroplasma, the intracellular parasite of Texas fever of cattle, to trypan blue, and the organism of malaria toward quinine, as to weigh down the scale in favor of their protozoan relationships. Here we would emphasize that the more we study these lower forms of life the more we become convinced that the "fixed idea" that any given living form must be either an animal or a plant has to be given up. These lowest forms of life are neither—or both. They must be regarded as **Protista**, as belonging to that nethermost kingdom from which in one direction animal forms, in the other plants, have been evolved.

PROTOZOAN PARASITES AS CAUSES OF DISEASE

There are certain parasites belonging to the division of the protozoa which can cause disease in man; these belong to different orders of protozoa; thus, for example, the entamœba is one of the sarcodiniæ, the trypanosome of the flagellata, the malarial organism belongs to the sporozoa, and *Balantidium coli* to the ciliate infusoria. One is tempted to try to find analogies between the protozoan parasites and the bacteria, but the development of ectotoxins by the protozoa is so slight and the toxins are of so low an order that it has not yet been possible to develop antitoxins or passive immunity by experimental means.

We have not yet enough knowledge of protozoan parasites to allow us to make general statements about them as a class, and we must be content to set forth individual points about the most important of these.

Order Sarcodiniæ.—Entamœba.—The *Entamœba histolytica* is a motile mass of protoplasm with a nucleus and a contractile vacuole which in appearance is similar to the amœba that inhabits ponds of stagnant water. The entamœba gains entrance to the colon, where it may set up dysentery; it attacks the mucosa and submucosa, ingests cell debris and red-blood cells, and may exist in great numbers. When it infests the bowel, its action is aided by pathogenic bacteria, which constitute a secondary infection. The entamœbæ are carried to the liver, where they often set up abscesses. More rarely similar abscesses

form elsewhere. There is a cycle of development in the colon which results in the formation of encysted stages; it is through these resistant forms, extruded in the feces, that the disease is transmitted. It appears that the cycle of development can be completed without an intracellular stage. It is not known that there is a toxin produced by the organism; the remote toxic effects seen in amœbic dysentery may be due to the secondary infection, or to the effects of cell disintegration.

FIG. 18
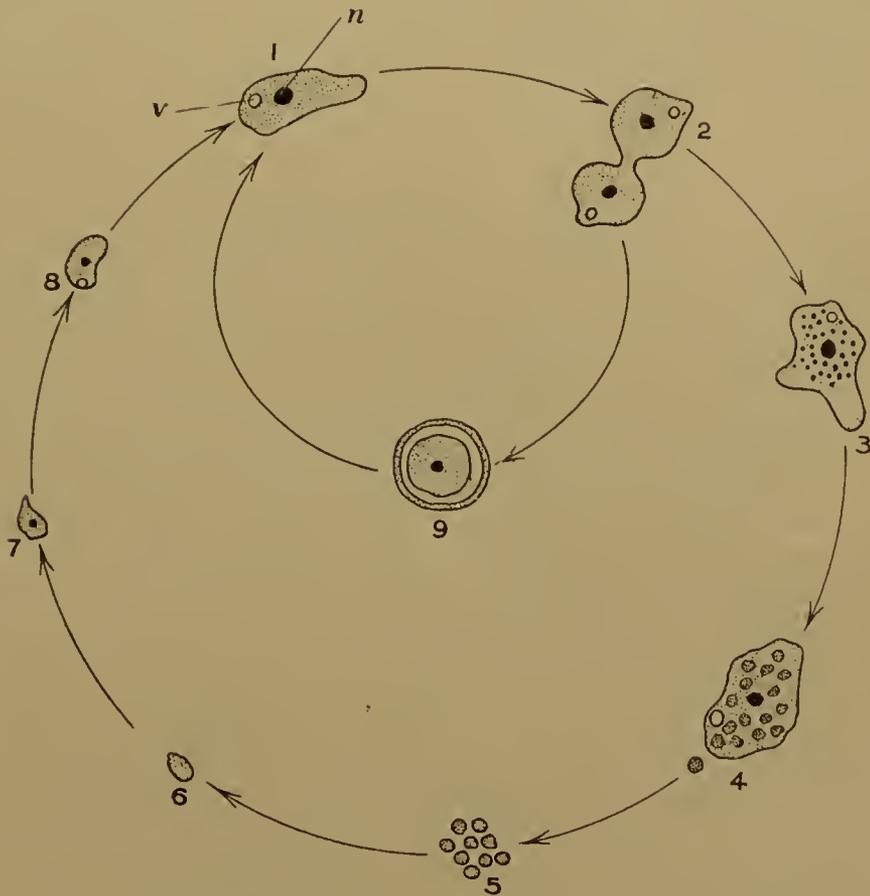
Schematic life cycle of the *Entamœba histolytica:* 1, the adult amœba with nucleus (*n*) and contractile vacuole (*v*); 2, the same, multiplying by amitotic division; 3, appearance of chromidial granules in cytoplasm, which enlarge and become the spores in 4; these spores become discharged or liberated (5) and develop (6, 7, 8) into the adult amœba, or (9) under other conditions the amœba passes into an encysted stage. (After E. L. Walker.)

Order Flagellata.—Of these, the trypanosome is a very important type. This is an elongated, spindle-shaped parasite with an undulating membrane along one side. It possesses two nuclei, a main nucleus and a **kinetonucleus**. From the **blepharoplast,** a minute chromatinic mass in juxtaposition with the kinetonucleus, arises a chromatinic filament which runs along the free edge of an *undulating membrane* and, in most trypanosomes, is continued beyond this into a free flagellum. A vacuole of doubtful function is often present close to the kinetonucleus. The dimensions of this protozoan may reach 30 or even 50μ, with a breadth of 2 or 3μ; and in freshly drawn blood it may be seen lashing to and fro in the field among the blood corpuscles like a wounded snake among dry leaves. In the vertebrate host the trypanosome

multiplies most often by longitudinal division; other methods of division have been described, but have been less studied. There is evidently not a little variation in the morphology and mode of multiplication of the various forms.

Trypanosomes are parasitic in all forms of animal life from the insecta to the higher mammalia. Many appear to cause no symptoms; others are highly pathogenic.

Civilization might overlook the 30,000 blacks who are estimated as the annual victims of sleeping sickness in West and Central Africa from *T. gambiense*, but deplores the millions of dollars annually lost from *T. evansi*, *T. brucei*, and other trypanosomes infecting horses

FIG. 19
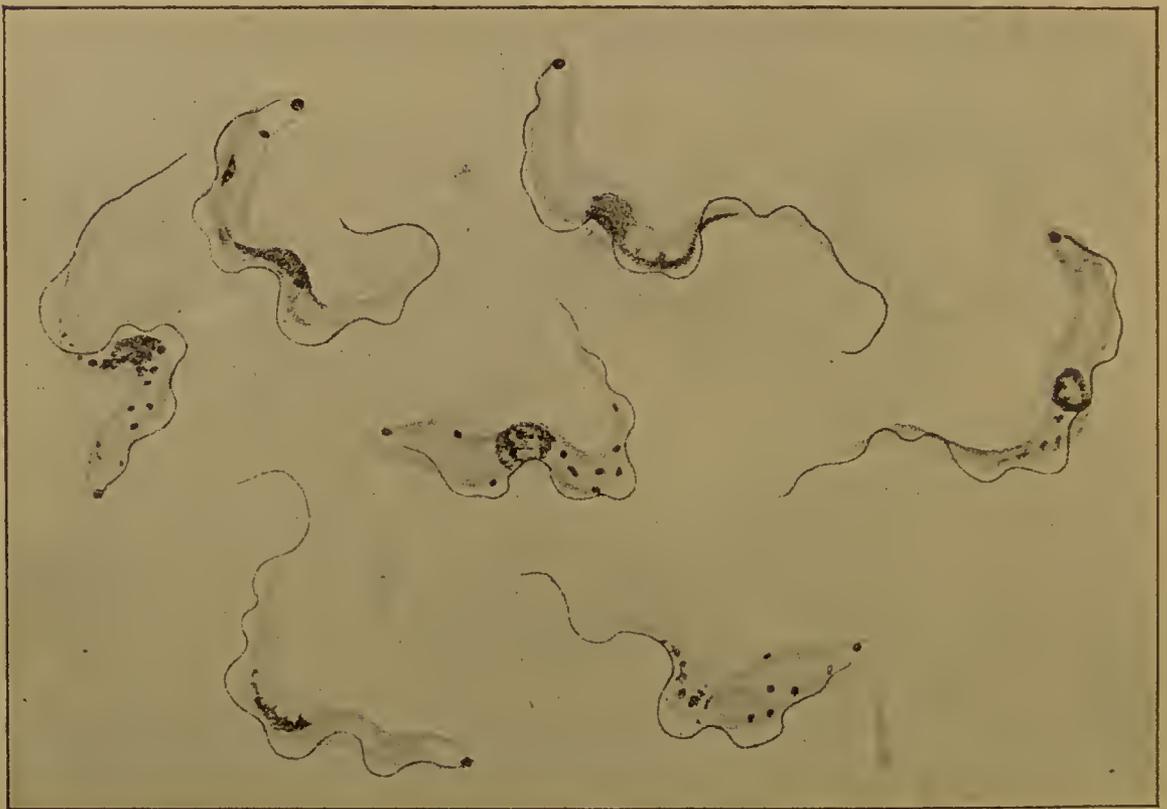
Trypanosomes (*T. gambiense*) from the blood in sleeping sickness.   × 2000.

and cattle. The forms of disease so caused are **surra** in Assam, India, and the Philippines; **n'gana** or **tsetse fly disease** in Southeast Africa; **dourine** or **mal de coit** in Algeria and Southern Europe, and in North America by importation, and **mal de Caderas** in South America. There is evidence that the trypanosomes of disease have a minute latent intracellular stage.

These forms of protozoa are conveyed to man and warm-blooded animals by the bites of blood-sucking parasites. Fish trypanosomes may be transmitted by leeches, those of warm-blooded animals by dipterous insects. Tsetse fly disease, which a quarter of a century ago invested this insect with all the fatality and mystery of a mediæval

EXPLANATION OF PLATE II.

PLASMODIUM VIVAX (TERTIAN PLASMODIUM).

Stained with Wright's modification of the Romanowsky method.

Fig. 1.—Young schizont, the so-called "ring-form."

Fig. 2.—Slightly older schizont.

Fig. 3.—Double infection of red corpuscle with schizonts.

Figs. 4, 5, and 6.—Young pigmented forms of the tertian schizont.

Figs. 7, 8, 9, and 10.—Tertian schizonts showing the division of the chromatin of the nucleus, enlargement of the infected erythrocytes, and increase in the amount of pigment.

Fig. 11.—Pre-sporulating tertian schizont.

Fig. 12.—Sporulating tertian schizont.

Fig. 13.—Free spores, or merozoites, of Plasmodium vivax.

Fig. 14.—Microgamete of Plasmodium vivax.

PLASMODIUM MALARIÆ (QUARTAN PLASMODIUM)

Stained with Wright's modification.

Fig. 1.—Young schizont, or so-called "ring-form."

Fig. 2.—Double infection of erythrocyte, with quartan schizonts.

Figs. 3 and 4.—Young pigmented schizonts.

Figs. 5 and 6.—Half-grown forms of Plasmodium malariæ, showing the division of the chromatin.

Fig. 7.—Pre-sporulating schizont of Plasmodium malariæ.

Fig. 8.—Sporulating schizont of Plasmodium malariæ. (Note smaller number of merozoites, and lack of enlargement of the erythrocyte, as in the tertian plasmodium.)

Fig. 9.—Free spores or merozoites of Plasmodium malariæ.

Fig. 10.—Microgamete of Plasmodium malariæ.

PLATE II

1   2   3   4   5

6   7   8   9   10

11   12   13   14

Plasmodium Vivax (Tertian Plasmodium).

1   2   3   4   5

6   7   8   9   10
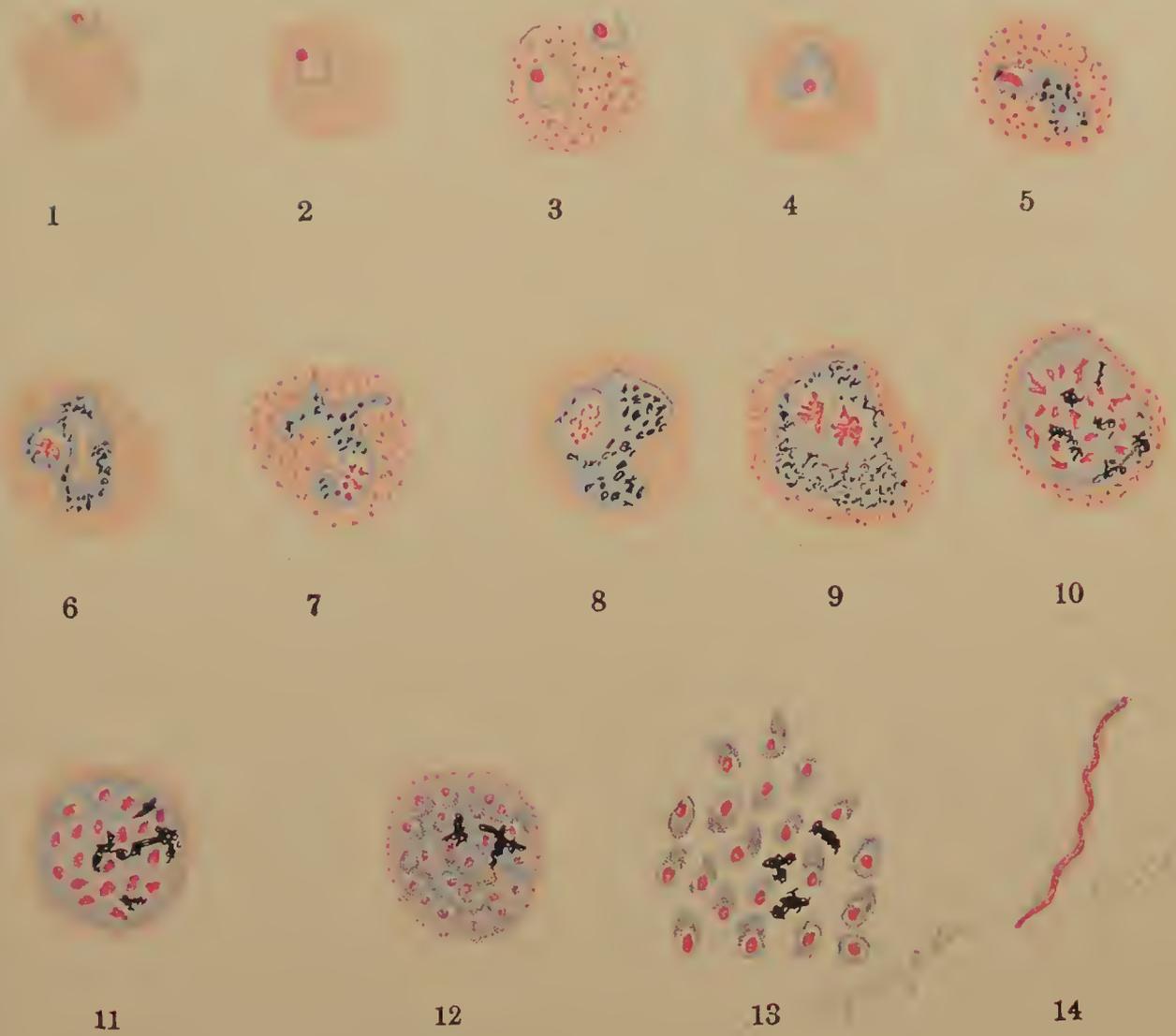
Charles F. Craig, Del.

Plasmodium Malariæ (Quartan Plasmodium).

dragon, is conveyed by **Glossina morsitans**, sleeping sickness by **Glossina palpalis**—blood-sucking flies. Taken up with the blood the trypanosomes undergo a development in the new host which varies according to the species. When their development in the fly is complete they are conveyed by the fly's proboscis into the tissues of a new host. There is a certain amount of evidence that they produce toxins, but the mechanism by which these induce symptoms has not been fully worked out. Those symptoms are anemia, glandular enlargement, circinate erythemas, moderate fever, the existence of œdemas, depression of cerebral activity and, finally, coma.

Fig. 20
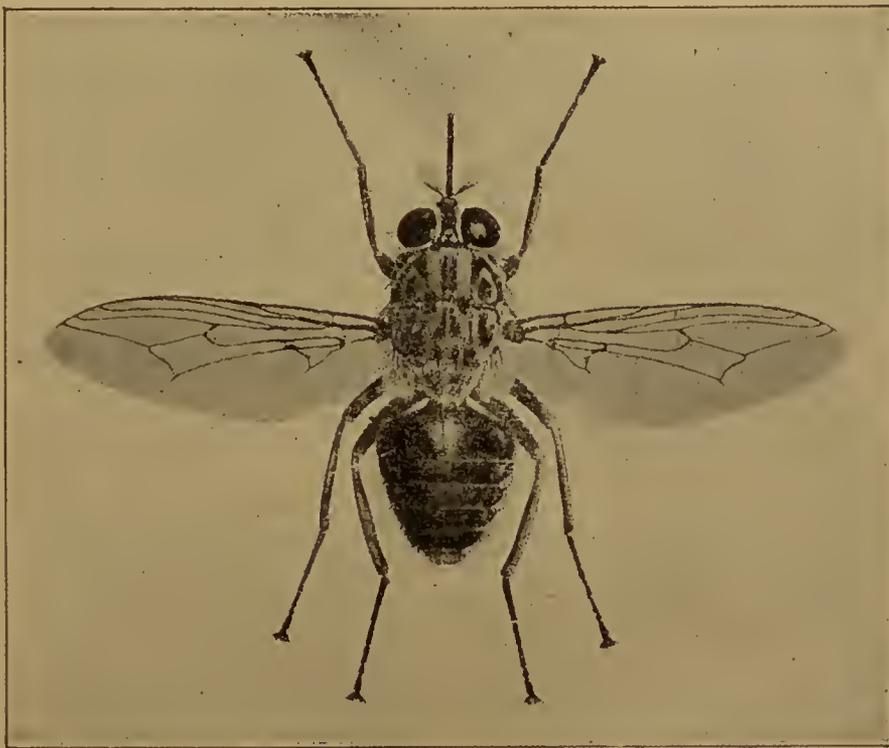
Glossina palpalis (× 33), the carrier of the trypanosome of sleeping sickness.

Other flagellata—the trichomonas and megastoma (*Lamblia intestinalis*)—are found in the intestine, but the cases in which they have been proved to be associated with disease are distinctly rare. The so-called Donovan-Leishman bodies found in the enlarged spleen in **kala-azar**, or **dumdum** fever of man, have been proved to have a stage in their life cycle in which they assume a *herpetomonas* form. The parasite is, therefore, classed now with the Flagellata, as is the allied body found in the sores known variously as Oriental sore, Aleppo button, etc.

Order Sporozoa.—Typical members of this order are characteristically intracellular. The parasite enters an individual cell, arrests its function and causes its death, the cycle of life of the parasite being such that the spore formation roughly corresponds with the time of death and disintegration of the host cell. The spores set free grow

into small amœboid forms, which enter other cells and repeat this asexual process. But a sexual cycle also exists, especially in the process of transmission from host to host, and this sexual cycle is carried out in the body of the carrier, which is of another species. In malaria, for example, the asexual cycle is carried out again and again in the human body; the mosquito (Anopheles) sucks infected blood, and the sexual cycle occurs in the body of the mosquito, the sporozoites, the products of the sexual cycle, being introduced into another human host with the proboscis of the mosquito, there to enter once more into a series of asexual cycles. Transmission by insects, though the most frequent, is not the only mode of transmission of sporozoa, for **coccidia** enter the digestive tract, and others supposedly by the respiratory tract.

Hemosporidia.—The parasite of malaria is the type of this suborder, and our knowledge of it has been greatly assisted by the study of allied forms in birds and other animals. The most important facts relating to malaria are these:

1. The disease is transmitted by certain anopheline mosquitoes, and is endemic or epidemic only where these are.

2. The Anopheles lays its eggs in still water, and the larvæ are aquatic; the mosquito does not travel far, save with high winds, and malaria is thus largely confined to the neighborhood of swampy or badly drained regions.

3. The Anopheles in general does not bite in broad daylight. Infection, therefore, occurs in the evening or at night.

4. The asexual cycle of development requires different periods of time for the different species of hematozoan—forty-eight hours for the organism of tertian fever; seventy-two for that of quartan; forty-eight (with irregular variations) for that of the estivo-autumnal type. The periodic chills and fever coincide with the maturation and sporulation of the parasite, the damage being probably wrought by the liberation of hematin and products of cell disintegration, when the host erythrocyte ruptures and the spores are set free, rather than by any specific toxin of the parasite itself.

5. The cell debris and pigment so liberated are carried to the spleen and there set up the changes that lead to the enlargement of that organ.

6. Prolonged asexual reproduction seems to weaken the parasite, so that if reinfection does not occur the disease gradually passes off. Yet it appears that the parasite may lie latent in the tissues for long periods and then become active again; clinical experience seems to show this especially in the case of the estivo-autumnal type. In malarious districts it appears evident that individuals gain a certain tolerance of the parasites, since they may have parasites in their blood without the symptoms which accompany infection in "non-immunes." Other sporozoa are unimportant, so far as the human race is concerned.

Order Ciliate Infusoria.—The *Balantidium coli* is found in the alimentary canal, associated with inflammation of the colon.

EXPLANATION OF PLATE III.

PLASMODIUM FALCIPARUM (TERTIAN ESTIVO-AUTUMNAL PLASMODIUM).

Stained with Wright's modification of the Romanowsky method.

FIG. 1.—Sporozoite, just attached to an erythrocyte.

FIG. 2.—Young schizont, the so-called "ring-form."

FIG. 3.—Double infection of erythrocyte by two young schizonts, or "ring-forms."

FIG. 4.—Fully developed "ring-form" of the tertian estivo-autumnal plasmodium.

FIGS. 5, 6, 7, and 8.—Developing schizonts of Plasmodium falciparum, showing increase in size, development of pigment, and division of the nuclear chromatin.

FIG. 9.—Pre-sporulating stage of Plasmodium falciparum.

FIG. 10.—Sporulating schizont of Plasmodium falciparum.

FIG. 11.—Macrogametocyte, or female gamete of Plasmodium falciparum. The so-called crescent form.

FIG. 12.—Microgametocyte, or male gamete of Plasmodium falciparum.

PLASMODIUM FALCIPARUM QUOTIDIANUM (QUOTIDIAN ESTIVO-AUTUMNAL PLASMODIUM).

Stained with Wright's modification.

FIG. 1.—Sporozoite just attached to the erythrocyte.

FIG. 2.—Young schizont, or "ring-form." Note very minute size.

FIG. 3.—Triple infection of the erythrocyte, with "ring-forms" of the quotidian estivo-autumnal plasmodium.

FIG. 4.—Fully developed "ring-form" of the quotidian species.

FIGS. 5, 6, 7, and 8.—Various stages in the growth of Plasmodium falciparum quotidianum, showing increase in size, development of pigment, and division of the nuclear chromatin.

FIG. 9.—Pre-sporulating schizont of the quotidian estivo-autumnal plasmodium.

FIG. 10.—Sporulating schizont of Plasmodium falciparum quotidianum. Note minute size of the spores, or merozoites, and the large amount of erythrocyte still preserved.

FIGS. 11 and 12.—Female and male crescents of this species. Note small size.

GAMETES OF TERTIAN AND QUARTAN PLASMODIA.

FIG. 1.—Young microgametocyte of Plasmodium vivax.

FIG. 2.—Well-developed microgametocyte of Plasmodium vivax.

FIG. 3.—Young macrogametocyte of Plasmodium vivax.

FIG. 4.—Fully developed macrogametocyte of Plasmodium vivax.

FIG. 5.—Flagellated microgametocyte of Plasmodium, the flagella constituting the microgametes.

FIG. 6.—Young macrogametocyte of Plasmodium malariæ.

FIG. 7.—Developed macrogametocyte of Plasmodium malariæ.

FIG. 8.—Young microgametocyte of Plasmodium malariæ.

FIG. 9.—Fully developed microgametocyte of Plasmodium malariæ.

FIG. 10.—Flagellated microgametocyte of Plasmodium malariæ, the flagella being the microgametes. Note the lighter staining of the male, or microgametocytes, and the different arrangement of the nuclear chromatin.

PLATE III
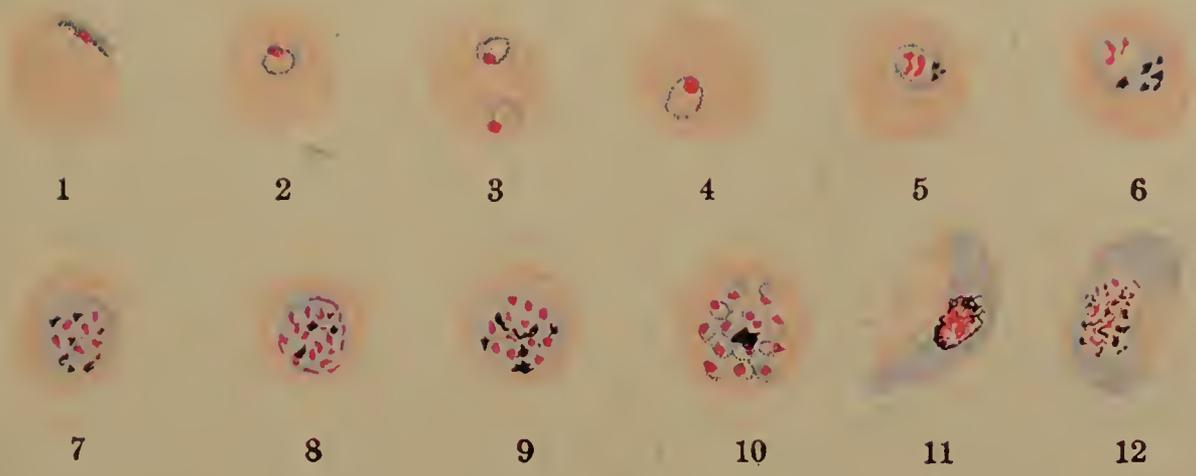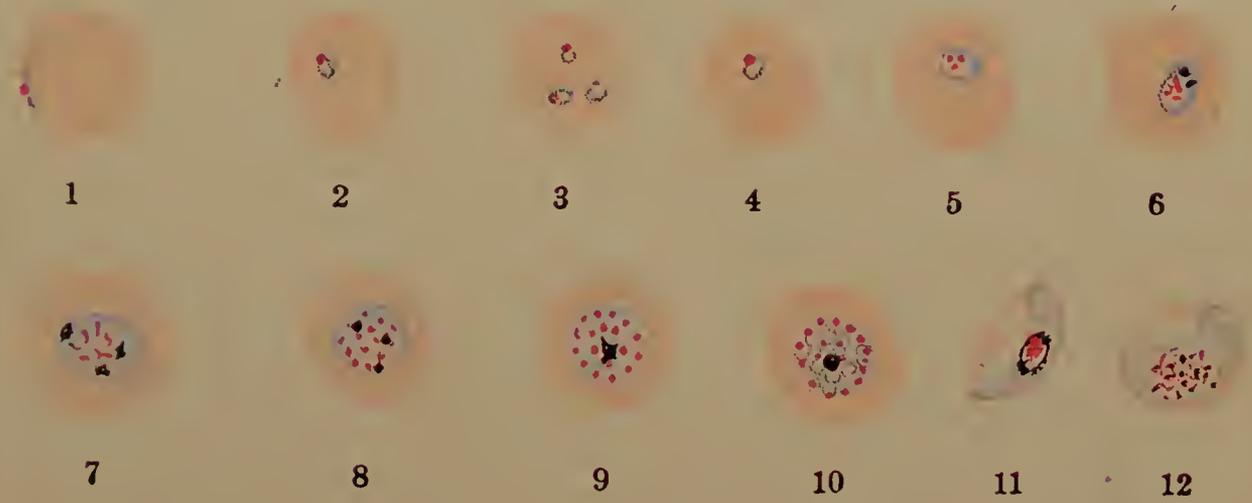
1 2 3 4 5 6

7 8 9 10 11 12

Plasmodium Falciparum (Tertian Estivo-autumnal Plasmodium).

1 2 3 4 5 6

7 8 9 10 11 12

Plasmodium Falciparum Quotidianum (Quotidian Estivo-autumnal Plasmodium).

1 2 3 4 5

6 7 8 9 10
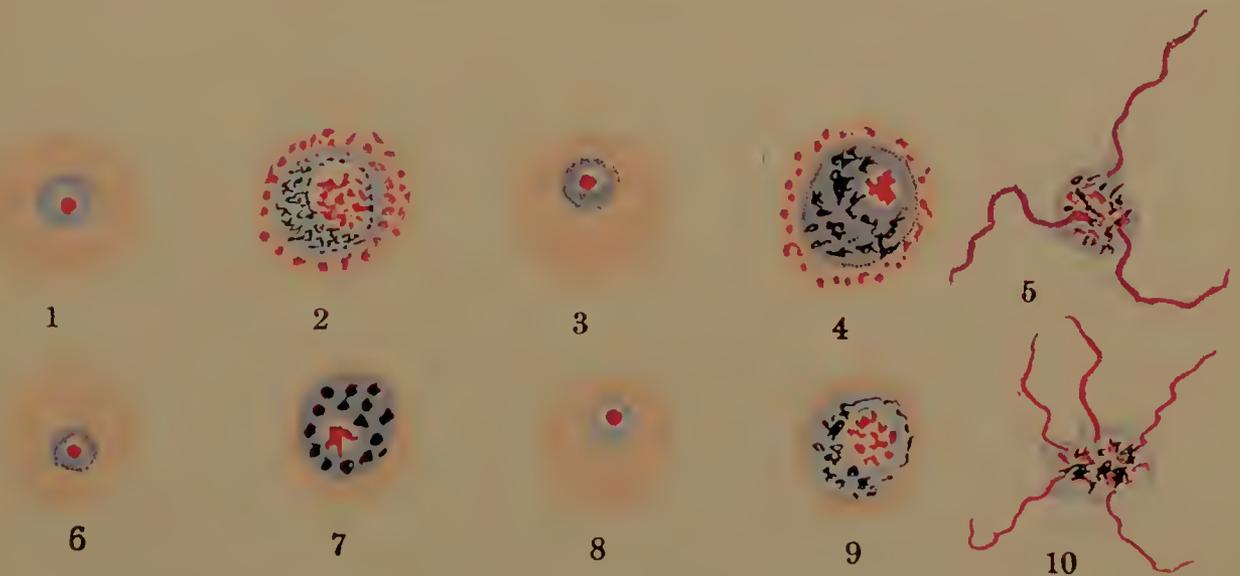
Charles F. Craig, Del.

Gametes of Tertian and Quartan Plasmodia.

METAZOAN PARASITES AS CAUSES OF DISEASE

The parasites of the metazoan order which are of importance as causing disease are of the classes of the *Platyhelminthes* or flat worms, the *Nemathelminthes* or round worms, the *Insecta* and the *Arachnidæ* (spiders).

The metazoan parasites, in general, take their food in a prepared state from their host, so that their digestive system need be only of the simplest sort; some, as the tapeworm, dispense with an alimentary tract and feed by absorption; their organs of locomotion need not be complicated; their organs of offence are only such as enable them to penetrate the body of the host to their food; their organs of defence are such as to protect them from digestion by the body juices of the host. A certain power to live apart from the host assures the continuance of the species, but this last is safeguarded best by their enormous reproductive capacity. Some of them are merely animated masses of reproductive glands, the quantity of ova being great, because most of it is destined to fall on barren ground. The simplicity of structure tends to greatly lessen the adaptability of the organism, so that we find that in the process of time a species becomes able to grow actively only in a particular species of host, or, if there is alternation of hosts, in a particular series of hosts. It follows, thus, that each particular species of host has a particular set of parasites.

The capability of causing disturbance in such forms is not great, a state of affairs which is to be expected with parasites of comparatively slow development. Such disturbance, too, is brought about in several different ways, as:

1. **Displacement or Pressure Due to the Presence of the Parasite.**— Although this is in general negligible, a *Filaria nocturna* may block a lymph vessel and cause elephantiasis of a member. A *cysticercus* in the brain may cause death, or the cyst of *Tænia echinococcus* in the liver may be very large, and may menace life.

2. **Injury Caused by Migration.**—The *filaria* migrates through the tissues but causes little or no damage in doing so; however, on the contrary, there may be much pain and inflammation of the muscles caused by the passage of larval *Trichinæ*.

3. **Destruction of Tissue.**—This is of very slight importance, and only to be considered in the case of a parasite like *Ankylostomum* opening up a large capillary, causing hemorrhage, or where a parasite like *Trichocephalus* boring through the bowel wall leaves a hole through which infection may pass.

4. **Loss of Food Material Used Up by the Parasite.**—Contrary to a common belief, this loss is so slight as to be negligible.

5. **Disturbance Caused by the Excretions of the Parasite.**—It has been supposed that the metazoan parasites excrete toxins as do bacteria; some of them certainly produce substances which protect them against the digestive juices of their hosts, and in many cases the bodies and

body juices of the parasites themselves are toxic, but this is to be expected, and does not give any additional proof upon the question at issue. More important is the fact that all verminous parasites set up **eosinophilia**, an increase in the number of eosinophile leukocytes in the circulating blood. This undoubted fact is evidently due to an excitation of the bone-marrow tissue by some irritant produced by the parasites, and it may be surmised that the anemia and the condition of ill-being are due to the same or parallel intoxicants.

6. **Nervous Irritation or Discomfort Brought About by the Presence of the Parasites.**—This refers mostly to the Insecta and Arachnidæ, and is an obvious, though unimportant effect; yet the presence of seat-worms and other migrating intestinal parasites may cause itching, grinding of the teeth, nervous irritability, and even convulsions in the very young.

THE ENDOGENOUS INTOXICATIONS

Internal Secretions.—There are certain glands, such as the liver, with external secretion, which form and discharge into the blood a further secretion, having no or little connection with the first. There are glands like the thyroid which, having no obvious secretion, and no duct, have been found, nevertheless, to discharge internally into the body juices secretions of great importance to the body. There are even structures that are not recognized as glands at all, such as certain sympathetic ganglia, which appear to form an internal secretion. And the end is not yet, for we know that certain portions of the mucosa of the alimentary tract have secretions, called **hormones**, which are necessary for the full activity of other digestive glands, even those situated at a distance. As distinct from enzymes, these hormones can be isolated in a state of relative purity and are *unaltered by heat*. In this class we include such bodies as adrenin and iodothyrin. Much of the information we possess about the internal secretions is yet fragmentary and we are not able to lay down general rules, but must be content to indicate some of the most important facts bearing upon the defect or excess of the same as factors in the production of morbid states.

Fig. 21

Cretin, male, aged twenty-one years.
(Bourneville and Bricon.)

Disturbances Related to the Thyroid Secretion.—Deficient thyroid secretion may show itself in the child as **cretinism**, or in the adult as **myxœdema**, the latter arising from mechanical removal of the gland (**cachexia thyreopriva**) as well as from more obscure causes leading to its atrophy, or interfering with its proper action. Cretinism is congenital; the cretin is physically and mentally in a state of retardation: the adult in years remains a child in intellect, or even an imbecile; dentition is late, and the sexual organs and functions delayed and imperfect; the stature is small, the limbs short and thick, the features coarse and expressionless.

Myxœdema developing in adult life has many similar features; there is a mucoid œdema (hence the name) of the subcutaneous and other tissues, gradually robbing the face of its expression; the features become heavy, and the subcutaneous tissue suffers a connective-tissue overgrowth. The skin becomes dry, the hair coarse, thick, and tending to fall out; the mentality becomes slow and the memory defective. The same train of symptoms may be set up by complete removal of the thyroid gland. Thyroid extract can cure myxœdema, and cretinism in the child, but requires to be given from time to time to prevent recurrence. It is to be noted that in some cases of myxœdema and cretinism, the thyroid, far from being absent, is enlarged; despite its size, we do not suppose that it functionates properly. It may be that the vesicles are expanded by secretion as the air sacs by air in emphysema, so that the walls and the bloodvessels are compressed, with resulting arrested absorption.

The opposite condition, clinically, to myxœdema is **exophthalmic goitre**, known also as Graves' disease and Basedow's disease; here one finds too much thyroid, or too active thyroid tissue, with resulting nervousness, tachycardia, tremors—features opposed in character to those of myxœdema. The striking features of the disease are the exophthalmos (probably due to irritation of the sympathetics), and the goitre. Tremors, great nervousness, and tachycardia may be present, indicating a nervous energy far different from the placidity of the myxœdematous patient. There is heightened metabolism and increased discharge of the products of tissue disintegration. Thyroidectomy often produces good results.

Disturbances Related to the Secretion of the Parathyroids.—Situated in or near or under the thyroids, varying in number, are small pea-like glands called the parathyroids, which histologically look not unlike the immature thyroid. Their removal in animals is followed by **tetany**, exophthalmos, rapid respiration, etc., which symptoms are ameliorated or removed by the use of calcium salts. This fact leads to the belief that they play an important part in regulating the calcium metabolism of the body. In many operations for thyroidectomy in the human being they are doubtless removed, without any apparent change being wrought, although the frequent presence of accessory thyroid and parathyroid nodules in the neck region makes it difficult to be sure in any individual case whether there has been complete ablation.

Disturbances Relating to the Secretions of the Pituitary Body.—The pituitary body is composed of an anterior glandular portion, a *pars intermedia*, containing both glandular and nervous elements, and a posterior nervous portion which is a continuation of the infundibulum. The glandular portion to some extent recalls the structure of the thyroid, since at times the cell collections take on a vesicular arrangement, the vesicles containing colloidal material. This colloidal material may escape or be passed through the intermediary and nervous portions into the third ventricle of the brain. It is the posterior particularly, and to some extent the intermediary, which afford an extract, or hormone, capable, like that of the medulla of the adrenal, of causing a great rise in blood-pressure, a rise more prolonged than that produced by adrenin. In addition the extract produces a marked polyuria, and, as Ott has shown, has a pronounced galactogogue effect, causing extraordinary increase in the secretion of milk. As shown by Cushing, stimulation of the posterior part is followed by glycosuria; removal, by an opposite condition of increased tolerance of sugar.

The effects of pituitary disease vary according as to whether they manifest themselves (1) prior to, or (2) after, adult stature is attained. Growths present in early life of the glandular portion, such as lead apparently to increased activity, are found accompanying a large number of cases of giantism. Such growths developing after adolescence are associated with the remarkable condition of **acromegaly**. This disease is characterized by increased development of the bones, more particularly of the face and the extremities, though the whole body skeleton is apt to be involved. With this overgrowth there is a corresponding development of the surrounding tissues. With enlargement of the maxillary and mandibular bones, the nose broadens, lips, ears, and eyelids enlarge. The hands and feet become, as it were, out of focus by being too near the camera. Other "neighborhood phenomena" such as hemianopsia and blindness are due to pressure of the enlarged pituitary upon the neighboring parts.

The opposite condition of **hypopituitarism,** if occurring in early life, is found associated with a form of infantilism and dwarfism with arrest of sexual development with or without pronounced obesity, increased tolerance of sugar, and at times liability to epileptic attacks. Developing in adult life there may be obesity with loss of sexual power, with the same tolerance of sugar and lowered mentality.

Just as in connection with the thyroids we not infrequently observe a condition of **dysthyroidism,** with some combination of symptoms of hyper- and hypothyroidism, so also we recognize conditions of **dyspituitarism.** In other words, overstimulation resulting in symptoms of overactivity of either organ may rapidly give place to symptoms of exhaustion and depression of function.

Disturbances Relating to Secretions of the Pineal Gland.—The pineal gland is the representative of the original median eye which, present in our more spider-like ancestors, can still be recognized in some of

the lizards and lower reptiles. In mammals this vestige has a more glandular character. Several cases are recorded in which tumors of this organ have led to disturbances of nutrition with increased growth of adipose tissue, and stimulation, with premature development, of the sexual functions and body growth.

Disturbances Related to the Secretion of the Adrenal and of the Chromaffin System.—The medulla of the adrenal, apparently the more important part of the organ, is related embryologically to the sympathetic ganglia. The extract of it (**adrenin**) leads to great increase in blood-pressure; it acts in part upon the vasomotor nerve system, but also directly on the plain muscle fibers of the arteries, contracting the arteries when the nerve endings are degenerated. The extract of the sympathetic ganglia has the same effect upon blood-pressure, and the effect of adrenin upon a part is identical with the result of stimulating the sympathetic fibers to that part. Both in the medulla of the adrenal and in the sympathetic ganglia is to be found a remarkable series of cells of sympathetic-nerve origin, the **chromaffin** cells, so called because of their affinity for chrome salts, the cells taking on a strong yellowish-brown color after immersion of sections in potassium bichromate. The indications are that wherever those cells are present, adrenin or a body having like effect upon the arterioles is also present. We use the term **adrenin** rather than **adrenalin** or **epinephrin** because the latter are names of proprietary substances.

There are several pathological states which, acting upon and destroying the adrenal, give rise to the disease known as **Addison's disease.** It is characterized by great physical weakness, feeble heart action and pulse, nausea, vomiting, and pigmentation of the skin. The pigmentation is most marked upon exposed surfaces, and in regions normally pigmented, and varies from a yellowish tint to a deep brown. Fibrocaseous tuberculosis, atrophy, malignant growths, hemorrhage, and inflammatory changes of the adrenal may produce it, and it has even been known to exist where the adrenals are healthy but the sympathetic ganglia diseased. It may well be imagined that the lack of blood-pressure-raising material due to the destruction of the organ accounts for the cardiovascular depression. As regards the cortex of this gland, it is interesting to note that just as overdevelopment of the glandular portion of the pituitary body is found associated with acromegaly and increased growth of skeletal tissues, so there are several cases on record in which hyperplasia and tumor growth of the adrenal cortex has been found associated with excessive and premature obesity, precocious muscularity ("infant Hercules"), and premature virility with precocious development of the external organs of generation.

Disturbances Related to Secretions of the Testes and Ovaries.—It is known that in castrated animals the secondary sexual characters fail to develop, and this is due, in the male, to the loss of large interstitial cells in the testes and of their internal secretion; there are homologous cells in the ovary, although the proof of the effect of their secretion is by no

7

means as clear as in the case of the male. "Heat" in castrated animals can be produced by the injection of the ovarian extracts. Not only do internal secretions of the testes and ovary affect sexual maturity, but they are also evidently concerned in the full physical development of the body. The function of the corpus luteum is of another sort; the secretion of the interstitial cells that lie external to the Graafian follicle is evidently potent to stimulate the uterine mucosa to respond to the presence of the ovum and permit its fixation; where the ovaries are removed after the fertilized ova are set free, these do not become adherent in the uterus. A secretion acting in this way is a good example of a hormone.

Disturbances Related to Various Other Internal Secretions.—*The Fœtus and the Mammary Gland.*—It has been proved, according to Starling and Claypon, that the hypertrophy of the mammary gland in pregnancy is due to the internal secretion, so to speak, of the fœtus. Watery extracts of rabbit fœtus injected into a virgin rabbit caused in a few weeks hypertrophy of the mammary gland and the formation of a thin fluid secretion; in multiparous, unimpregnated rabbits this was true milk. To disprove the supposed effect of nervous influences, a mammary gland in the guinea-pig was transplanted to the region of the ear, where it underwent hypertrophy in pregnancy, and, finally, produced milk. It is thought that the substance in the fœtus which does this acts upon the mammary gland causing anabolism and growth; when the child is born, lactation begins because this substance is no longer present, and the cells which before, under its influence, manifested anabolism and growth, in its absence break down and form milk. Thus lactation is apt to cease with the onset of a new pregnancy.

Doubt has recently been thrown upon these observations, other observers associating the growth and activity of the mammary gland with the corpus luteum of pregnancy.

Disturbances Related to Secretions in the Intestinal Tract.—It is but recently that we have discovered how intricate a system of internal secretions exists in the alimentary tract, and we shall rather try to indicate what these are than to deal with their derangements. The acid contents of the stomach passing into the duodenum cause an increase in the flow of pancreatic juice; this happens not because of reflex nervous stimuli, but because of a chemical substance which is secreted by the duodenum and carried by the blood to the pancreas. If the mucosa of the duodenum is scraped off and an extract made of it with hydrochloric acid added, this extract, which has been called **secretin,** if injected into the blood of a mammal, causes an abundant secretion of pancreatic juice. In a somewhat similar way the secretion of pyloric glands stimulates certain glands in the cardiac portion of the stomach; these instances enable us to surmise that not only does nervous mechanism stimulate the flow of digestive juices, shown by the mouth "watering" at the sight or smell of food, but also that there exists a series of secretions developed by the mucosa of one part

after another, each of which secretions can, if absorbed by the blood, excite to secretion some neighboring part of the tract. Of what are the diseased conditions of the tract due to absence or perversion of these secretions, we can as yet only conjecture.

Disturbance Related to the Internal Secretion of the Pancreas.—Apart from its digestive secretion, there appears to be an internal secretion of the pancreas; without recapitulating the proofs that exist, we may state that this secretion, a true hormone, being put into the blood enables the liver and the muscles to properly handle carbohydrates. We are able to say this much: (1) the normal pancreas forms a **prosecretin**; (2) the liver and muscle are the main seats of deposit and utilization of carbohydrates; (3) that, unassisted, they cannot break down these carbohydrates; (4) that with its help they can convert soluble carbohydrates into insoluble glycogen and *vice versa;* (5) that it is the secretin of the pancreas which acts as a hormone and activates or renders capable these tissues. This explains why the extirpation of the pancreas in dogs leads to glycosuria, and why certain lesions of the pancreas in the human being are followed by diabetes; but there remain many cases of diabetes that are not as yet at all explicable.

To recapitulate briefly the points we have been considering, we have, in all these disturbances due to improper action of internal secretions, a problem into which two or more factors enter; there is first, the internal secretion, second, the substratum or substance on which it acts, and third, in many cases, a hormone by virtue of which it acts. Disturbance may occur (1) by diminished secretion with normal amount of substratum; (2) by normal secretion with excess of substratum, and (3) by absence or diminution of the hormone without which the interaction cannot happen. Thus in (1) the lesion may be in the organ supplying the secretion, in (2) in the organ supplying the substratum, and in (3) in the organ supplying the hormone, and it is conceivable that in all three cases the symptoms might be the same. Further, it deserves note that the work of the last few years is indicating that the healthy state of the body is largely dependent upon the **interaction** of the secretions of the ductless glands; that, to a certain extent, one ductless gland and its secretion can replace another. The reader will have noticed the parallelism between the adrenal and pituitary bodies, each formed of a glandular and a nervous area, the active principle in each more intimately associated with the nervous portion, though the indications are that the glandular portion plays a part in the development of the active principle. Structurally, a likeness may be traced between the thyroid and anterior glandular tissue of the pituitary, and as a matter of fact atrophy or removal of the one is found to be followed by hypertrophy of the other organ. A similar intimate relationship is to be noted between the functional activities of adrenal, thyroid, pituitary body, and pineal on the one hand, and of the testes and ovaries on the other. Hyperactivity of the chromaffin system,

also, is seen to lead to glycosuria, presumably through influence upon the pancreas. We are coming to recognize increasingly the existence of a **polyglandular** syndrome, to see, that is, that disturbance of one of these organs of internal secretion is surely associated with disturbances of the others.

Non-eliminated Products of Katabolism.—Intoxications may be caused by these in two ways: either the excretory organs, being diseased, fail to eliminate products of katabolism or even if the secretory organs eliminate, there may be resorption of the excreted material owing to obstruction in the ducts.

The Resorption of Excretions.—There is a normal resorption of excreted material constantly going on in the body; the feces solidify in the lower bowel because of resorption of fluid; the increase in solids in gall-bladder bile over that of hepatic-duct bile indicates absorption, while some physiologists hold that urinary water is reabsorbed as it passes down the tubule; this suggests that there are many series of cells which work in two directions, that is, which excrete in one direction, and absorb in the reverse direction. An example of this resorption to a serious degree is found in obstructive jaundice; here the bile is not discharged, and is reabsorbed by the lymphatics and the blood. Accompanying such jaundice are certain cerebral symptoms, slowed pulse, itching of the skin, lessened coagulability of the blood, and a tendency to hemorrhage. Some of these symptoms can be set up by the experimental injection of bile salts, although normally these bile salts are reabsorbed in the alimentary tract, whence, however, they are carried once more to the liver by the proper channel. It is the resorption at the wrong place of such an excretion as the bile salts that causes the disturbance, rather than their deleterious nature, *per se.* The same statement holds with regard to the pancreatic juice, which, if reabsorbed by reason of the obstruction of the pancreatic duct, can set up pancreatitis; while, if bile be absorbed by the pancreas from a blockage of the ampulla of Vater by a calculus or by spasm of the same such as occurs when the gall-gladder is removed, or the cystic duct obliterated, a yet more severe pancreatitis may ensue.

Certain cases of **uremia** are to be viewed in the same way. Uremia may be due to renal incompetency, where dangerous constituents fail to be abstracted from the blood, but in other cases, the kidneys perform their part, but the ureter or the urethra is blocked, and the urinary epithelium passes back into the blood materials from which it had previously freed the blood. What the substance or substances may be that cause uremia is yet unknown, though many different ones have been suggested.

Disintegrative Intoxications.—**Autolysis.**—This is the process of self-disintegration that tissues undergo; if, for example, liver tissue be removed from the body and protected from septic infection, it becomes soft, by reason of enzyme actions, the most important of which is that one which breaks up proteins. To illustrate this, one may take the fol-

lowing figures (Wells): a liver in which only one-tenth of the nitrogen was in a soluble form, after being kept twenty-two days aseptically, contained six-tenths of its nitrogen in a soluble form. The enzymes which bring about this change are elaborated within the cells them-selves, and all soft tissues behave in this way, the liver and renal cortex among the most active, the brain substance and skin among the least so. Autolysis occurs most readily in a slightly acid medium and at a temperature slightly higher than that of the body. The tissues are naturally alkaline in reaction, and the process begins only when this alkalinity has been neutralized by the production of carbon dioxide and organic acids, such as lactic and butyric, which are formed in dying tissues. This process of autolysis takes place in the living organism. Thus, if a piece of liver have its blood supply cut off, autolysis will occur in the more central parts, but not in the per-ipheral, because the alkaline lymph diffuses into this part of it. There is, however, an exception even to this, viz., wherever leukocytes gain entrance in large numbers. Leukocytes possess enzymes, the **leuko-proteases**, which act most powerfully upon the leukocytes themselves, but once liberated act also upon other tissues. This explains the softening of septic infarcts, and of the outer zone of simple infarcts, into which areas great numbers of leukocytes migrate; it explains also the softening and absorption of the exudate in a pneumonic lung. Lymphocytes have not these strong proteolytic enzymes, and so lymphocytic exudates do not show the same autolysis; there is, for example, no such softening and absorption of the exudate (of lympho-cytes) in (tuberculous) caseous pneumonia. The softening of a tissue by the effect of this leukocytic enzyme is called **heterolysis**, as opposed to *autolysis*, where the cells of the part themselves supply the enzyme. But, to prevent this universal heterolysis wherever there are leukocytes, there is an antibody in blood-serum which tends to neutralize the enzyme of the leukocytes, provided these be not present in overwhelming numbers (Opie).

Autolysis is seen in the liver in cases of acute yellow atrophy, phos-phorus and arsenic poisoning, chloroform poisoning, and in the group of cases characterized by pernicious vomiting (oftenest cases of preg-nancy). In these the end-products found in autolysis are present, viz., leucin, tyrosin, etc. The operative toxin has evidently destroyed the cells without destroying their ferments.

There is a partial explanation possible at this point of gangrene as it occurs in diabetic cases. **Acidosis**, as it is called, is a condition of heightened acidity or lessened alkalinity of the tissues, with the production of acetonuria; such is frequently present in diabetes, and this lessened alkalinity permits the occurrence of autolysis, although the gangrene is probably precipitated by associated obliteration of the vessels of the part.

Autolysis is able to cause certain disturbances of body mechanism, which can be classed as (1) disturbances due to liberation and diffusion

of the enzymes, and (2) disturbances due to toxic action of the diffused products of autolysis. It is quite likely that in some cases both actions are at work. **Albumosuria** is an indication of such a diffusion, the albumoses appearing in the urine when there is extensive aggregation of leukocytes, with its accompanying heterolysis, such as happens in the resolution of pneumonia or in empyema; albumoses appear also when large tumors undergo softening or necrosis. **Fever**, too, as it occurs in infarcts, internal hemorrhages, burns or suppuration, is an indication of the liberation of intracellular enzymes; the experimental production of fever by ferments of all orders injected into the blood has been often demonstrated. Rarely the production by autolysis of acutely toxic substances occurs. Cholin is liberated in the autolysis of nerve tissues; it is not highly toxic, but it is readily converted into neurin which is. Cholin has been found in the cerebrospinal fluid of cases of nerve degeneration and softening, and it is suggested as the cause of convulsions and other serious disturbances that happen in these subjects (Mott). Perhaps a similar formation of toxin from the disintegrated cells is accountable for the toxic manifestations seen in cases of severe superficial burns.

Impaired Metabolism as a Cause of Disease.—At times the cells of certain organs of the body do not carry out the process of metabolism to its normal termination, and discharge substances that are toxic, or, through deficient oxidation, there may accumulate in the system, bodies not themselves toxic, but obstructive to the proper activity of the tissues. At other times, although metabolism can scarcely be said to be impaired, yet the metabolites fail to be excreted, and by their accumulation tend to cause disease.

Gout.—Gout is a condition characterized by attacks of acute arthritis and other constitutional symptoms: clinically, by the excess of uric acid in the blood, and anatomically, by the deposit of sodium biurate in the cartilages and elsewhere. It must not be imagined that this excess of uric acid in the blood is the cause of the disease, for uric acid in excess exists in the blood in a number of different states without gout being present. The urates are inert bodies, and the most that can be said is that they are an **indicator**; that is, the faulty metabolism which produces them produces also substances that are toxic. These substances we do not know with any exactness.

Uric acid is one of a group of substances called **purin bodies**, of all of which, purin ($C_5H_4N_4$) is the nucleus. These bodies are **uric acid, xanthin, hypoxanthin, guanin, adenin,** and so on. By some they are termed the **alloxuric bodies,** and (with the exception of uric acid) sometimes the xanthin, purin, or alloxuric bases. These bodies are derived from nuclein, which shows that they originate from the disintegration of nuclear substance. This nuclear substance may be from the food (meats), in which case the purins are *exogenous*, or it may be from the nuclear substance of the tissue cells of the body, in which case they are *endogenous*. There is normally a certain small output of

endogenous purin bodies which represents the natural wear and tear of tissue. The muscles are constantly putting out hypoxanthin, and exercise increases the output of uric acid, suggesting that one purin body is readily converted into another in the body, as happens *in vitro*. If the pancreas be chopped up and allowed to act on guanin, it can convert guanin to xanthin by means of a ferment which has been called **guanase**. Similarly, adenin can be converted into hypoxanthin by the adrenal, the thymus, the pancreas, or the liver, by the action of the ferment **adenase**. The different glands, in fact, contain ferments or groups of ferments; and in this series a ferment, an **oxidase**, is found in the lungs, liver, muscles, and spleen, which can convert the alloxuric bases into uric acid. Yet another oxidase, found in the kidneys, the liver, and the muscles, can oxidize uric acid into urea. Finally, or perhaps one should say firstly, there is in cells generally a **nuclease** by which nucleoproteins are disintegrated, liberating the purin bases.

Step by step the following process can be seen to occur: (1) nucleo-proteins, exogenous from foodstuffs, or endogenous from the body cells, acted on by *nuclease*, yield (2) purin bases, which, acted on by *guanase* or *adenase*, yield (3) xanthin and hypoxanthin, which, acted on by an *oxidase*, yield (4) uric acid, which, acted on by an *oxidase*, yields (5) urea.

There are other much more important sources of urea; but this will indicate the variations in the amount of uric acid that may be derived from the same diet, and the importance of the action of certain ferments that are constantly present in the body.

It is necessary to know, more fully than we do, the toxic effects of the purin bases, for they are toxic, and it is perhaps the purin bases that are responsible for gout. Gout, therefore, is probably *the outcome of insufficient oxidation*, whereby the precursors of uric acid, and similar bodies, are not fully oxidized, and by their accumulation and their toxicity, set up morbid changes; and the uric acid formed is in its turn imperfectly oxidized, and accumulates; *this diminished oxidation is due to a constitutional deficiency of oxidases, inherited or acquired*.

Cystinuria.—The appearance of cystin in the urine is an unimportant matter, save that it may lead to calculus formation; but it is worthy of note at this point, as somewhat parallel to gout. It tends to be a familial disease, characterized by the appearance of **cystin** in the urine. Cystin is a sulphur-containing amino-acid, and the evidence seems to show that it arises from an abnormal disintegration or conversion of the sulphur-containing part of the protein molecule.

Alkaptonuria.—This condition, in which the urine turns dark on exposure to the air, is due to the absence or deficiency of a specific oxidase with the result that final oxidation of the aromatic constituents of the protein molecule is imperfect. It, again, is unimportant clinically.

Obesity.—The accumulation of fat in the tissues is not a toxic manifestation, but follows an incomplete oxidation of the foodstuffs; when it brings about impairment of locomotion, the oxidation process becomes yet more incomplete, and the ill is cumulative. The normal fate of fat in the body is to be burnt up, yielding ultimately carbon dioxide and water, and a fixed amount of heat and energy; in obesity, fat is stored up to such a degree that 38 per cent. of the total weight has been found to be fat. This state of obesity is due either to (1) excessive absorption of food, either fats or substances, like carbohydrates, whose katabolism yields fats, or to (2) inadequate combustion of the fats so acquired. A given case of obesity may be due to both; but in those cases of obesity which show anemia, deficiency of hemoglobin and corpuscles, it seems likely that deficient oxidation is to blame.

In the plethoric, obese man, who has no such deficiency, the explanation is either overeating or an hereditary tendency to store up fat upon a normal diet; such an hereditary tendency is often combined with goutiness, and just as the goutiness means imperfect oxidation of one group of the products of metabolism, the proteins, so the obesity may mean imperfect oxidation of another group, the fats.

Acidosis, Acetonuria, etc.—The group of cases which show lessened alkalinity of the blood, and the accumulation of **acetone** and the **acetone** bodies (β-**oxybutyric** and **diacetic acids**) in the blood, is characterized, in general, by grave intoxication, air hunger and nervous symptoms, leading even to coma and death. We cannot as yet say definitely what is the origin of these bodies, whether from the amino-acids of the protein molecule, from the fatty acids or from the carbohydrates; perhaps in different diseases the source may differ, for acetone and the acetone bodies appear in diabetes, in hyperpyrexia, in wasting diseases, in cancer, and in starvation; carbohydrate starvation seems to be a constant factor, whether this arise from actual lack of carbohydrates or from impaired ability of the body to use what it does receive.

The accumulation of β-oxybutyric and diacetic acids in the blood of diabetics seems responsible for the main symptoms of diabetic coma, for herbivorous animals to which they are administered develop the same group of symptoms—the blood is less alkaline, they are stuporous, dyspnœic, the blood is bright red and contains less carbon dioxide than normal. If alkalies be given the symptoms pass off, just as may occur clinically in diabetic coma. The explanation is that normally the alkalies of the blood take up carbon dioxide from the tissues, carry it to the lungs, where by the help of the oxidase present, the carbon dioxide is split off, and the salt, once more basic, is prepared to take up more carbon dioxide from the tissues. Where there is excess of acids in the blood these combine with the basic salts, and as a result the carbon dioxide remains in the tissues, causing symptoms of asphyxia.

Before leaving this subject, it may be recalled to the reader's mind that this condition of acidosis seems to underlie the disturbances found not only in diabetic coma, in certain cachectic diseases, and

in starvation, but also in the pernicious vomiting of pregnancy, the cyclic vomiting of children, chloroform poisoning, and certain other less common states where grave hepatic disturbance has been determined; at the present time we can do no more than state the observation.

Dyspnoea and Asphyxia.—These symptoms, it will be seen, depend upon acidosis. It was for a long time debated whether they were caused by deficiency of oxygen or excess of carbon dioxide, and the decision is in favor of the latter. The tension of oxygen in the inspired air may be reduced from 20 to 8 per cent. without inducing dyspnoea, but an increase of tension of 0.5 per cent. of carbon dioxide in the inspired air and so in the blood, leads to such increased activity of respiration that the volume of inspired air is doubled. Be it noted that the increase is not in the *amount* of carbon dioxide in the blood, but in the *tension* of free carbon dioxide in it; for in diabetic coma, as has been said, acids combine with the alkalies present in the blood plasma, and less carbon dioxide is actually taken up; but it still diffuses in the blood, and is present in a free state, giving rise to the asphyxia.

Eclampsia.—There is a most grave condition which occasionally shows itself during the last few days of pregnancy or in the few hours immediately following parturition. It appears in the form of convulsions, followed by coma, and frequently is fatal. Postmortem examination shows that there are two orders of cases; in the one there is extreme degeneration of the kidneys, in the other, the brunt of the disturbance is seen to have fallen upon the liver, which exhibits areas of degeneration even to complete necrosis of the parenchyma of the organ. The condition is essentially associated with childbearing, is not of infectious nature, but has all the ear-marks of a grave intoxication, but as to what is the exact nature of the intoxication, we are still wholly in the dark. While some attribute it to the foetus, others bring (inadequate) evidence that the toxic material originates from the placenta. Others, again, ascribe it to want of balance between the internal secretions of the maternal organism. The latest suggestion is to compare it with the milk fever of cattle, and as this last can be cured in a remarkable way by distending the udders with air, which acts, it appears, by reducing the circulation through and absorption from the mammary glands, so eclampsia may be due to resorption of cell disintegration products elaborated in the production of the milk. We are not in a position to classify properly the condition.

INTOXICATIONS NOT PURELY EXOGENOUS OR ENDOGENOUS

Gastro-intestinal Intoxications.—It is a common observation that constipation in a person whose habits are regular induces a feeling of lessened well-being, and, it may be, actual headache and malaise—in a person whose habits have become irregular it may be so pronounced

that he is unmoved for several days, but this without grave disorder being the result. The malaise in the first case is best explained as due to absorption of toxic substances from the intestinal canal. Herter has shown that **indol** introduced into the tissues sets up headache, muscular weakness, and sense of fatigue, conditions resembling those ascribed to constipation. Now indol is a tryptophane derivative— a product of protein disintegration: it is formed, for example, by the proteolytic activities of the colon bacillus, and along with cresol and the ethereal sulphates is absorbed, more particularly in obstruction of the upper part of the small intestine, being discharged into the urine as indican.

This is stupidly termed **auto-intoxication** by many writers. So far as we can see there is not the slightest evidence that the indol is produced either from the tissue cells, or even by the digestive juices. The only possible known auto-intoxication of gastro-intestinal origin is by β-**imidazolylethylamin,** a highly toxic derivative of histidin, which can be isolated from the mucosa of the duodenum and upper part of the small intestine; but some hold that this again is produced by bacterial agency. The fact that it is easily obtainable from the normal mucosa indicates that normally it fails to be absorbed; possibly in obstructive cases it may accumulate and set up serious symptoms.

The indications are that many of the grave symptoms of chronic constipation and obstructions are of the nature of low infections rather than intoxications.

Among the decomposition products of proteins due to bacterial activity are the **ptomaines.** These form a large class of substances obtained from the decomposition of animal matter; they are **diamins,** the results, although not the ultimate results, of the disintegration of proteins, for if the decomposition be continued beyond a certain time the ptomaines diminish in amount, giving place to simpler substances. The well-known ptomaines are **methylamin, di-** and **trimethylamin, cholin, neurin, muscarin, cadaverin,** and **putrescin.** They are found in certain bacterial putrefactions, but in very minute quantities, so that there is grave doubt whether they play any part in alimentary intoxications.

Diseases of Defective Nutrition.—For long years confusion has reigned regarding certain diseases which have been recognized to follow defective nutrition. As to the exact nature of the defect there was no unanimity of opinion. In the old days of sailing ships it was recognized that, however abundant and varied the food—necessarily preserved—given to the sailors, they were apt to suffer from **scurvy,** with purpuric eruptions, softening, swelling, and bleeding of the gums, shortness of breath, intense weakness, etc. In Japan and the Malay peninsula, among those living mainly upon rice, a disease was, and still is, common and fatal, known as **beriberi,** characterized by paresis of an ascending type, with œdema and weak heart action, muscular pains, and progressive loss of weight, in which at autopsy the only

striking anatomical change is a degeneration of the peripheral nerves. Sometimes in poorhouses and asylums and in fishing fleets off the banks a very similar disease shows itself, **ship beriberi.** With the increasing employment of patent foods and sterilized milk for babies, a new disease has shown itself—**Barlow's disease** or **infantile scurvy,** characterized by agonizing pain upon moving or even touching the limbs, accompanied by swellings upon the long bones due to periosteal hemorrhages, with, in addition, cutaneous and other hemorrhages, loss of weight and inanition. All these conditions, when not too advanced, can be arrested by affording change to a diet of fresh food, particularly fresh fruit or fruit juice, and fresh, uncooked vegetables; or in the case of Barlow's disease, fresh as distinct from sterilized milk along with orange or grape juice.

Until recently there was complete ignorance as to what caused cooked and preserved foods and prepared grain, like rice, to lose their nutritive qualities and set up these disturbances. The first step toward solving the problem was taken by Axel Holst, of Christiania, by demonstrating that feeding fowls and pigeons with an exclusive diet of canned or salted meat, or upon prepared grain, he could induce in them within a very few days an extensive degeneration of the peripheral nerves—**polyneuritis gallinarum**—with progressive paralysis. He draws attention to the similarity between the experimental disease and ship beriberi as seen among Norwegian sailors. Independently Braddon, in the Malay peninsula, renewed the old theory that Oriental beriberi is due to an exclusive rice diet, calling attention to the fact that this disease attacks those living upon polished rice, but not those whose diet consisted of the unpolished and unhulled rice. Acting upon his suggestion, Fraser and Stanton, using for their experiments prisoners condemned to death, found that as a fact they could set up beriberi in those fed almost exclusively upon polished rice, and could arrest it if they now added to the diet the polishings or bran discarded in preparing the rice for sale; nay, more, could arrest it by administering an alcoholic extract made from these polishings. *Evidently, therefore, the outer coat, or pericarp of the rice grain, which is removed in polishing, contains a something essential to nutrition.* This "something" is not a proteid, a fat, or a carbohydrate. Its recognition renders it evident that **we have to add another essential element to the diet necessary to sustain life.** It is affected by heat (over 100° C.), and becomes slowly inactive by keeping. What is more, while having none of the physical properties of an enzyme, it is effective when present in most minute quantities.

To this new factor Funk has given the name **Vitamine,** and using large amounts of material, he has been able to make a preliminary chemical determination of its nature. Thus 380 kilograms (over 700 pounds) of rice polishings afford 215 grams of a curative vitamine, reduced to 1.8 grams on recrystallization. From this and the vitamine obtained from 100 kilograms of dried yeast he obtained nicotinic acid

(m. pyridin-carboxylic acid), probably a decomposition product of the vitamine, though this in combination with another product ($C_{24}H_9O_9N_5$) seemed essential for arresting polyneuritis in pigeons.

The observations of Funk indicate that these vitamines have a marked influence in building up the phosphatides. The brains of pigeons fed on vitamine-free diet are distinctly reduced in their nitrogen and phosphorus contents. The degeneration of the peripheral nerves appears to be connected with disintegration of the myelin sheaths, rather than of the axis-cylinders.

Yet another disease may possibly have to be placed in this category. It is an old belief that **pellagra**, with its train of cutaneous and nervous diseases, is associated with a diet in which corn (maize) is a predominant factor; whether it plays a part is very hotly debated at the present time. It is at least a curious coincidence that in the United States, with more perfect systems of milling, the vitamines are removed from the flour to a greater extent than in Italy with its more imperfect methods, and that whereas the milder chronic form of the disease is common in Italy, the acute form is frequent in the United States.

The moral to be gained from these observations is not that we are to eschew the use of white bread, corn flour, canned meats, and sterilized milk, but that we are to *shun their too exclusive use*. The dietary should contain green vegetables, fresh fruit, fresh milk, and meat; these afford sufficient vitamines, if taken daily along with the preserved and prepared foods which, today, form so important a part of our diet.

BODILY STATES AS DIRECT AND PREDISPOSING CAUSES OF DISEASE

Overstrain.—Overstrain and fatigue are the results of work, with the difference that while **fatigue** is the natural, physiological sequel of activity, **overstrain** goes a step farther and indicates an abnormal degree of fatigue or a pathological effect wrought by activity; **exhaustion** goes farther yet, and implies overstrain carried to such a point that continued activity is impossible unless a period of rest intervene.

Everyone knows by experience that fatigue is a natural consequence of work and demands rest; if adequate rest be obtained, fatigue disappears, and the worker is left better able to work than before—the result being that in course of time that maximum state of ability to work is reached in which we term the worker or the athlete "trained." If, however, the rest be not adequate, or if work be carried to such an extent that the fatigue is excessive, or if the work be of the nature of violent effort—the return to the normal is secured only after a rest unduly prolonged, because we have gone past mere fatigue and have got "overstrain." Further, the person or organ that has experienced the overstrain is the worse for it, is not stronger from the exercise, but is less capable of responding to a given demand. Practically, this is becoming daily of more importance to the physician, and an

understanding of the principles of work, fatigue, overstress,[1] and rest is essential to him. Whether work and fatigue concern more the nervous or the muscular mechanism matters not; in either case, if the work done equal in units of energy the food taken in, the body does not suffer, because the energy that the body possesses is like a bank account, to which there is a daily income and from which there is a daily draft; if day by day the amount drawn out exceeds the income, the account diminishes, and a sudden large call upon the account will require many days of income with careful expenditure before the amount of the account is restored. The reader can supply other analogies in the same line of thought; and we may be forgiven for the digression if we recommend every practising physician and every student to read the classic "Rest and Pain" of Hilton, which excellently demonstrates how valuable a therapeutic principle is judicious inactivity.

The results of overstress are various according to the organs involved and to the degree of overstress; there is either direct production of a morbid state, or an increased susceptibility to disease.

Direct Production of Morbid States by Overstress.—The degrees of overstress have been classified as superacute, acute, and subacute; they will be considered in this order.

Superacute overstrain has not lacked examples since the soldier dropped dead at Athens after gasping out the news of Marathon. There are all gradations from this down to the few moments of suffocating breathlessness of the "commuter" who has had to run hard to catch his morning train. The symptoms of the lesser grades of superacute overstrain seem largely due to cardiac inadequacy, the heart not being able to pass on the blood as rapidly as the muscles demand. The cases in which death follows intense prolonged strain suggest in many ways that there are discharged into the blood toxic products of muscular activity. Cadaveric rigidity immediately follows death; the dark venous blood fails to coagulate; the capillaries are dilated. The acute degree of overstrain may be excited in such a case as where a man not in training is severely indisposed after a mountain climb; he has anorexia, fever, pain in the limbs, and is restless and sleepless. From longer-continued, but less extreme effort, come such results as writers' and pianists' cramp, and the labioglossal paralysis of flute players; and there are undoubtedly local and general manifestations of disturbance from overstress of the ocular muscles in their attempts to keep accommodation perfect.

Overstress as a Predisposing Cause of Disease.—It is long known to clinicians and experimenters that overstress makes the subject of it more liable to infection, that hard work, long hours, and inadequate rest make men more liable than normal to acute diseases, such as influenza and pneumonia. If resting animals and animals undergoing forced labor are subjected to the same doses of bacterial cultures,

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[1] Over*stress* is the physical cause; over*strain* the bodily state produced by it.

the resting animals resist much the better; if into any such animal, along with the culture, lactic acid be introduced, the bacteria grow the more readily; this is interpreted to mean that the acid produced by the muscular activity of the exhausted animal assists the growth of certain bacteria in the tissues.

In a way entirely local, also, overstress renders the organ concerned specially liable to disease, and this is true not only of overstress, but also of stress; in the fœtus, the right heart bears the brunt of the circulatory work, and in the fœtus cardiac disease is right-sided; subsequent to birth, the stress on the left side of the heart is greater, and heart disease tends to be left-sided. It is notable in this connection, too, that vegetations grow on the heart valves as a result of infection plus stress; the entire surface of the valve is exposed to the insult of the infection, but the entire surface of the valve does not develop vegetations; the area near the valve edge where one valve strikes the other in closing is the part that is exposed to both the insult of infection and the insult of stress, and here it is that the vegetations develop.

The last-named principle works in both directions, so that not only are "strained" organs, or parts thereof, liable to infection and other damage, but infected or damaged areas are more liable to overstrain than healthy ones, or, stated otherwise, what is merely stress for healthy tissue is overstress for damaged tissue. It is the subjects of chronic intoxications, such as syphilis or alcohol, in whom the ordinary work of the circulation produces aneurysmal and other evidences of vascular overstrain.

Muscular Fatigue and Overstrain.—Muscular fatigue has been considered by some as fatigue of the muscle fiber; by others, as fatigue of the nerves concerned; it is one or the other or both. The muscle itself can be fatigued by direct stimulation, because the substances produced by contraction inhibit further activity; when the nervous mechanism is considered we cannot experimentally fatigue the conducting axone; nor can we fatigue perceptibly the reflex centres in the cord; but what we do observe is this: if a reflex centre for a particular muscle be selected, a centre that is amenable to influences from several afferent tracts, and we stimulate one of these tracts, we produce in time the phenomenon that the muscle no longer responds; if, now, another afferent tract be employed, the muscle at once responds. This shows that the muscle itself is not exhausted, nor is the axone exhausted; what is exhausted is the **synapse**, the junction between the afferent nerve tract and the nerve cell of the reflex centre; these two are parts of different neurones. Let us here digress to give a "working idea" of the connection between neurones. One nerve cell does not actually join another nerve cell, but we may say that it is in contact or almost in contact with it; terminal filaments of one cell are in "almost contact" with the dendrites of another, like the branches of one tree intermingling with but not actually touching the branches of another; impulses skip across the space from twig to twig, when they are in a

state of "almost contact." Fatigue of a nerve cell may be practically thought of as a shrinking, by which the twigs or branches of one are drawn away from the other, so that impulses have farther to jump from one to another than before, and do so less readily; if cells are fatigued, the impulses pass poorly because of this withdrawal from contact; with sleep we may suppose that the rested dendrites or axones are expanding out once more to a position of almost contact; so that on waking, the impulses (or thoughts or whatever they may be) pass readily once more. Reverting to the specific example we are considering, we may imagine that the constant stimulation of one afferent tract makes the processes of that neurone draw away till the impulse no longer readily jumps the gap, and the neurone governing the muscle is no longer

Fig. 22

A   B
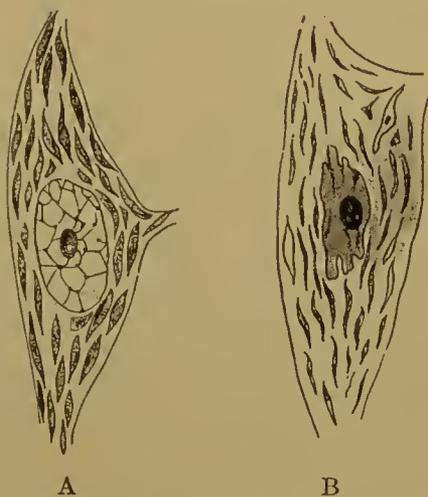
A, resting nerve cell with large rounded nucleus, showing chromatin network, the Nissl bodies in the cytoplasm (derived from the nuclear material), also large and prominent; *B*, exhausted nerve cell of same order, with shrunken irregular nucleus, chromatin network indistinct, Nissl bodies diminished in size and poorly staining. (After Gustav Mann.)

stimulated; the state of "almost contact" is lost, the "synapse" fatigued; when a new neurone is used, which is in "almost contact" with the neurone governing the muscle, the impulse passes readily, and the neurone and the muscle respond.

Fatigue of the muscle itself appears to be due to the formation of products of muscular activity—sarcolactic acid, carbonic acid, and others. These substances have effect probably also on the nerve mechanism; and finally, we have to admit that nerve cells themselves are capable of organic change through use—that even the process of reasoning tires—although the experimental proof is not to be obtained. This exhaustion of the neurone has been well demonstrated by Hodge and others by comparison of the staining power of nerve cells and nuclei in rest and after prolonged activity.

Lack of Activity and Disuse as Causes of Disease.—Tissues atrophy if unused, and the atrophy so produced is not in any sense different from the atrophy that follows diminution of blood supply to a part; the most that can be said is that tissues in activity tend to have a good

circulation, adequate nourishment and prompt removal of waste products. All this is lacking in muscle whose nerve supply is cut off, and amid these various coincident circumstances it is not possible to say which is most responsible. A word is necessary here about so-called trophic nerves; these were supposed to be fibres which had special governance over the nutrition of the tissues; but the atrophy or other derangement of tissues separated from central control need not be due to the section of trophic nerves, but may surely arise from lack of properly governed activity, from consequent inadequate food supply because vasomotility is not rightly governed, from delayed removal of waste products. Since perfect health of tissue depends upon the right coördination of nutrition, vascular supply and cell activity, it seems reasonable to suppose that the lack of this coördination may be attended by actual tissue alterations and by increased liability to infections.

PREDISPOSITION AND SUSCEPTIBILITY

By these terms we mean an abnormal liability to be influenced by some environing factor, whereby a morbid state is set up. Living under different conditions, it has come about that no two of us respond in exactly the same way to the same external influence; even in an individual, different tissues respond with varying degrees of reaction to the same stimulus. Sensitiveness above the degree that is usual is susceptibility or predisposition. As was shown earlier, this predisposition may be inherited or acquired.

Inherited predisposition may be (*a*) **specific** or **ex specie**, as is shown by the predisposition of cattle to pleuropneumonia, dogs to distemper, man to gonorrhœa and typhoid. Or it may be (*b*) **racial**, as seen in Europeans and yellow fever, Hebrews and diabetes, or it may be (*c*) **familial**, as in certain exanthemata, particularly neuroses, and gout.

It is necessary to digress at this point to indicate that error may easily occur here. A family may really be comparatively immune to a disease because, by survival of the fittest, the stronger members of the family have, by virtue of some characteristic, been able to resist a disease to which they were liable and have been enabled to hand down this characteristic strengthened. But where a disease has been endemic, there are many individuals who have acquired, in an unnoticed manner, their immunity. They have had unrecognizable or unrecognized mild attacks of the specific disease which have sufficed to protect them. This is seen in the apparent immunity of the natives of many countries to malaria, the children when examined having the malarial parasites in their blood. Nay, more: they may only have taken in minimal amounts of the infection, which their tissues have overcome, and in this very act they have manufactured an immunity because they have been constantly attacked by minimal amounts of the toxin.

In an infectious hospital it is often noted that where diphtheria is being cared for, attendants are liable in the first few days to sore throat, but should no actual attack of diphtheria supervene, they are often found to be subsequently immune. The presumption is that they absorb a small number of diphtheria bacilli frequently, and that these stimulate them to build up an immunity to the disease.

Classification.—Predisposition may be classified according to:

1. **Sex.**—The female is exposed to a series of disorders connected with menstruation, childbirth, and the menopause.

2. **Life Period.**—*Infancy.*—Disorders of maldevelopment and inanition (to the end of first year); athrepsia, various forms of enteritis with diarrhœa; meningitis.

Childhood.—Rickets, measles, scarlatina, diphtheria.

Puberty and Adolescence.—Chlorosis (in female); acute rheumatism and rheumatic heart disease (ten to fifteen); typhoid; tuberculosis.

Adult.—Typhoid (twenty to twenty-five); tuberculosis (twenty to thirty).

Middle Age.—Gout, lithiasis, and chronic Bright's disease (thirty-five onward); arteriosclerosis, aneurysms (thirty to fifty); cancer (forty to sixty).

Old Age.—The same continued, along with atrophic conditions.

3. **Habit of Life at Different Life Periods.**—In the years of infancy when growth is proceeding rapidly, the digestive system is under most stress; limited power of locomotion prevents much exposure to infectious diseases, which occur at a later time when the child mingles freely with his fellows; the age of work produces often a more sedentary life in more confined and often less well-ventilated surroundings (the period of tuberculosis); with increasing age, lessened exercise and yet more sedentary life tend to constipation, gallstone formation, etc.

4. **Previous Infection.**—Although in some diseases an attack confers immunity, there are others in which there remains a greater liability to a second attack; such are erysipelas, furunculosis, acute rheumatism, and influenza. It may be that the germs of the disease are not destroyed, and that a low state of general health permits them to flourish once more. Not only this, but an attack of one disease is frequently followed by an infection of a different kind, as when one exanthem is immediately followed by another.

5. **Malnutrition.**—To exemplify how malnutrition predisposes to disease, it is necessary only to cite the severe epidemics of infectious disease that, at different times, have followed upon famine in Russia, India, and Ireland.

The Susceptibility of Particular Tissues.—Reference is made here not to the susceptibility of an area that is injured or badly nourished, for this has been already dealt with, but to the fact that certain tissues are prone to permit the growth of certain infectious agents. The channel of entrance has something to do with this, so that inhaled germs often attack the respiratory, and ingested germs the digestive tract. In

8

foci that are clearly secondary, and evidently selective, we find the tubercle bacillus growing readily in the pia-arachnoid, but infrequently in the brain; infrequently in the stomach, and often in the small intestine. Even if injected into the blood stream, colon bacilli are apt to set up enteritis. The fact of the susceptibility of special tissues remains, but we have no adequate explanation for it. Consideration of these data brings us to an important conclusion that *an infection does not involve the whole body. Coincidently with the growth of the specific germs in individual organs, there tends to be a reaction to and destruction of the same in other parts.* We find typhoid bacilli in a patient suffering from that disease, in the spleen, liver, skin, and kidneys, but with much difficulty in many other organs; yet we know that the infection is a universal one, and that these other organs have their chance to become infected. It seems that in susceptible regions the bacteria are winning, and in others losing their battle with the tissues.

Idiosyncrasy.—This term is applied to the exhibition of extreme susceptibility to the influence of substances that are not hurtful, and even beneficial to the average of people. Strawberries, shell fish, certain fish, in some people cause urticaria or other skin eruption, headache, and in fine, indications of an intoxication; idiosyncrasy to drugs is familiar to every physician. Hay fever is an idiosyncrasy to one or more particular kinds of pollen; and the presence of a cat in the room, although unseen and unthought of, produces in some people a state of nervous apprehension, explicable by some unperceived olfactory impression; these as yet are curious facts lacking explanation, save that the recent study of the phenomenon of **anaphylaxis** has introduced us to a possible explanation of at least some cases. The administration of minute doses of protein followed, after a few days, by larger doses of the same protein, results in a general systemic disturbance resembling that seen in some of these cases of idiosyncrasy—malaise, profound depression, coryza, erythematous and other eruptions on the skin, or even in some cases severe respiratory distress of an asthmatic type, the phenomena, in short, of "**serum sickness.**" It is evident that the system may develop an extraordinary susceptibility toward one or another protein, by the exhibition of relatively minute quantities of the same. The food idiosyncrasies, hay fever, and some cases of asthma seem thus to come into line with serum sickness and anaphylaxis in general.

CHAPTER III

THE MORBID AND REACTIVE PROCESSES PROPER

THE LOCAL REACTION TO IRRITATION—INFLAMMATION

It is very necessary for the student to obtain a clear understanding of what inflammation is, and how it begins, progresses, and ends, because a large fraction of all the pathological specimens he will ever see and a majority of the clinical cases he will be called to treat involve in some way this process. He can become conversant with the thousand special cases of inflammation only by knowing that the same general laws underlie them all, even those most diverse in appearance.

In whatever member of the animal kingdom we examine it, the response to an irritation is similar; if we scratch the tissue of an invertebrate with a needle, certain effects are produced; if we scratch the skin of a human being we find effects that at bottom are similar; in other words, the tissues from their simplest to their most complex type have learned only one way to behave when they are irritated or injured; the complex body has more ways of exhibiting its reaction because it has more differentiated tissues, but the process we see in the simplest

animal we find also in the most complex animal, and it is this unity that makes it possible for us to construct certain rules which underlie every case of inflammation.

Inflammation is the series of local adaptive changes in tissues that result from actual or from referred injury. By injury we mean all grades of stimulus, from a mere irritation which only quickens the activity of the cells, to a damage which kills or all but kills them; and we insist upon some such understanding of the term inflammation; because those who work in a special field are apt to restrict the term, and here the physician, the surgeon, the physiologist, and the medical student must meet on a basis common to all; the tissues behave after the same manner whether they are injured by the aseptic knife of the surgeon,

FIG. 23
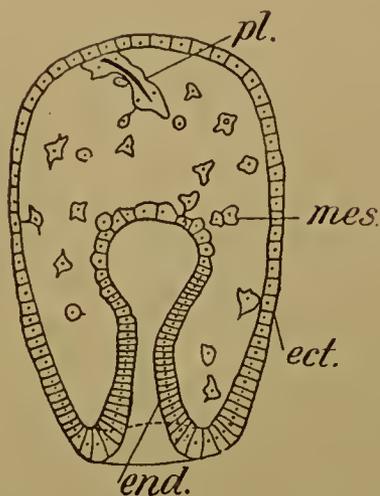
FIG. 24

Larva of one of the simplest metazoan forms (*Astropecten*) to show *ect.*, ectoderm; *end.*, endoderm; *mes.*, wandering mesodermal cells which at *pl.* have attached themselves to a foreign body and formed a plasmodium around it.
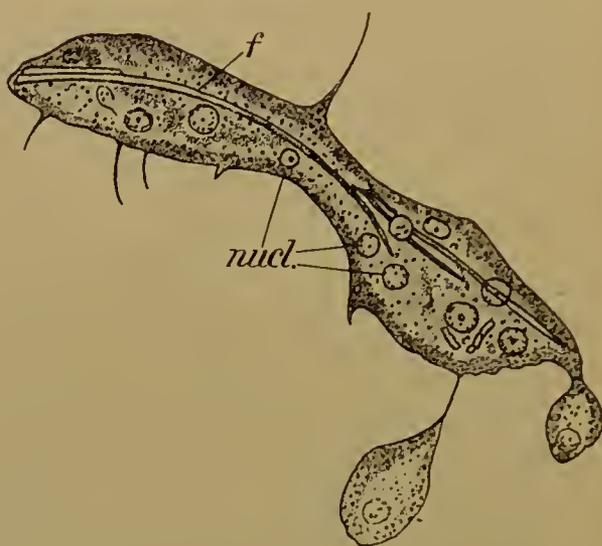
The plasmodium of fused mesodermal cells seen in the previous figure, higher magnification; *nucl*, nuclei of individual cells. (After Metchnikoff.)

the poison of the Staphylococcus aureus, the flame or the frost, and it would be wrong for us to lay down restrictions that nature has indicated so definitely to be false. There are those who say that inflammation of a wound occurs only when infection invades it; not so; the wound itself implies inflammation; and this broad view of the case, having priority and right upon its side, has two good reasons for being admitted. There are those, on the other hand, who go even farther than we, and say that inflammation includes not only the changes at the site of injury, but every other change in the body at large that accompanies this; this is apt to confuse the learner, and the distant changes will be dealt with by us in considering *general reaction to injury and infection;* so that we restrict the term inflammation to the **local** changes in any tissue that reacts.

The process of inflammation, occurring in the invertebrate animals,

we shall touch upon merely to illustrate two fundamental principles, two modes of defence against injury, and at the same time two modes of repair of the damage inflicted, for thus early in our consideration of the subject, it is necessary to show that the processes—inflammation and repair—are inseparable. These two principles are (1) that sooner or later a **proliferation of cells of the part** concerned occurs, and (2) that there is a **determination of wandering cells** to the injured area.

If we take the simplest form of cœlenterate, we find a differentiation into ectoderm, endoderm, and mesoderm, as in Fig. 23. The mesoderm cells are formed from the other layers, and represent what will become, in higher forms, the supportive structures of the body;

Fig. 25
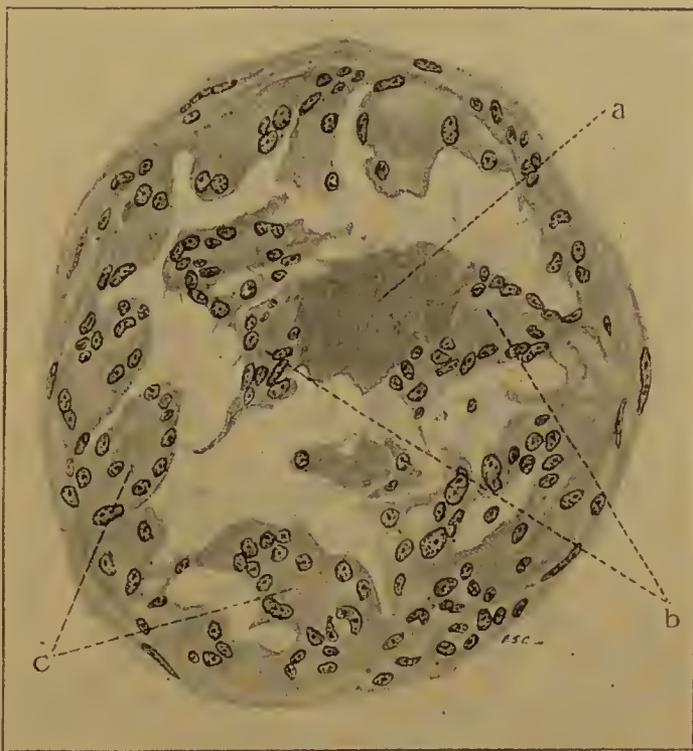
Foreign body giant cells in thyroid vesicle, to show similar plasmodium formations surrounding foreign body, or its equivalent, in man: *a*, remnant of mass of colloid in centre of vesicle; *b*, giant cells attacking the colloid; *c*, giant cells that have already dissolved colloid. (From case of chronic interstitial thyroiditis, Dr. Rhea.)

it will be noted that in this simple form they are either relatively *fixed* or *free*, some being joined loosely by cell processes, others wandering. If an irritant body be introduced into this cavity the cells travel toward it and stick to it; its very presence irritates to reproduction cells in contact with which it lies, and thus new cells are born; these cells, new and old, surround it and if it be digestible, they digest it; if not, they fence it off and render it as harmless by this isolation as they can. Here are both principles illustrated, positive **chemiotaxis**, or attraction, and **cell proliferation**. This must be kept in mind later on when we find that the wandering cells, mesoblastic in origin, are the cells that

exhibit chemiotaxis and rally to the site of injury, whereas the fixed cells of the body tend to proliferate and regenerate.

As we advance farther up the zoölogical scale to those animals that have an open vascular system, but no proper vessels, we find another fundamental principle illustrated; if the ectoderm be punctured, the lymph which bathes the cells of the body coagulates and temporarily seals the hole; this is to be remembered when we find in our studies on the human body that a scaffold of fibrin is constructed throughout the injured area. As we advance once more to the higher animals, which have a closed vascular system, we find that these same simple features persist, and that the vessels serve to convey more readily and more rapidly lymph and wandering cells to the injured part, there to carry out their functions—the same functions that we find their counterparts performing in the lowly organized cœlenterate.

The detail of the inflammatory process must be dealt with farther on with more particularity.

The Causes of Inflammation.—1. **Bacterial.**—Bacteria are most frequently the exciting cause of inflammation, whether by their direct action in originating the process, or as an adjuvant to trauma, as in infection after a wound, or as in secondary infection after a burn or after the action of some corrosive. It becomes at once evident that this admits a very large number of bacteria to our consideration; there are the pathogenic organisms, such as the Bacillus typhosus or the Streptococcus pyogenes, which can inaugurate inflammation; there are the saprophytic organisms which cannot grow in the body normally, but which can multiply in surface discharges or on mucous membranes, and there liberate toxins which can be absorbed and cause inflammation; the non-pathogenic forms are able to do nothing of this kind and for our purposes are negligible.

If we are dealing with a microbe capable of setting up or of assisting to set up the process of inflammation, it is by no means certain that the inflammation will be of a definite, fixed degree of severity; every case of bacterial inflammation is a problem in which it is necessary to gauge the virulence of the organism and the resistance of the patient; and we shall see that varying grades of intensity and rapidity of the process are thus set up.

Bacteria may attack the body directly, being carried to and implanted upon it from the outside, or from the mucous surfaces of the throat or intestine, just as the Æsopian viper bit the countryman who warmed it in his bosom. Another form of infection is of great clinical importance. It sometimes happens that an operation wound, made with the most careful asepsis, becomes infected; it is possible that there may have been some fault in technical work, and the bacteria may thus have come from the outside; but it may also happen, and does happen, that the patient supplied the infection himself, and that bacteria were carried from some of his storehouses, the throat or the intestine, by way of the blood to the wound, because

the wound is at the moment the part of least resistance in the body. This implies that there are bacteria in the blood; such we believe actually to be the case. It is true that blood cultures of the healthy yield no growth; nevertheless, there are indications that from time to time bacteria are being picked up from the upper air passages and from the intestine, and that under ordinary conditions these are rapidly destroyed by the agency of the blood and endothelium; but if living bacteria be carried to a part where the resistance is low, as a wound, then in place of undergoing destruction they are able to make a foothold and multiply. One very important function of the liver is to kill off the bacteria carried from the intestine in the portal blood; for the portal blood picks up not only food particles from the bowel but also organisms, whose remains can be found in the liver at any moment. It is true that the bacteria which escape into the blood are quickly destroyed by several agencies, and the internal organs are *potentially*, if not actually, sterile. It is these "chance" organisms which cause the **latent** infections and the **terminal** infections, which last so often supervene upon some chronic disease; an example of this is that a man dying slowly of heart disease is generally found to harbor some inflammatory process such as pneumonia, which arises not by infection due to highly pathogenic microbes brought in from without, but from bacteria, often of low virulence, which hitherto have been impotent to obtain a foothold within the tissues. In such a case the resistance is at a low ebb, and a small number of bacteria of low virulence doubtless suffices.

The process of inflammation is caused not by the mere presence of bacteria but by the effect of the toxins given off from them. To use a homely example, one may think of each bacterium or group of bacteria as surrounded by a little halo of toxin which it gives off either during its life or at its death and lysis through the action of the cells and tissue juices; the tissues lying within the influence of this toxin becoming inflamed. The cells which face the toxin in its least diluted form suffer the most severely and the cells farther away in a constantly lessening degree.

2. **Traumatic.**—Inflammation may be set up by a very numerous class of physical agencies; the surgeon's knife, a blow, a crush, a puncture, friction, movement (reëxciting an inflammation that has subsided), electricity, heat, and cold are all capable of injuring or killing cells; the cells, once killed, have to be got rid of and their dead bodies themselves are irritant by reason of the chemical products of the disintegration of protoplasm; so that in every case of trauma we have two factors assisting one another in the production of inflammation. When the minimum of destruction is wrought, as in an aseptic wound, we have the process of inflammation in a simple form, viz., the series of events which we call **repair**.

3. **Chemical.**—Strictly speaking, the products of bacteria are chemical causes of inflammation, but under this heading we deal with substances or gases which have a destructive effect on tissues; it is a familiar fact

that antiseptic solutions have the power to kill and injure cells to a certain depth; and the action of certain products of the animal and plant body is well known, *e. g.*, the venoms of insects and reptiles, cantharides, mustard, and croton oil.

3. **Nervous.**—Nerves can not only stimulate tissues, but can irritate them, and we find tissues that undergo inflammation solely from this cause. Herpes zoster is a well-known example; this follows upon irritation and inflammation of one or more posterior root ganglia; again, at times the cheek becomes swollen, red, and painful, in short, inflamed, because a tooth in the area of distribution of the same facial nerve is the seat of trouble; this is the form of inflammation we had in mind when we defined inflammation as a reaction to **referred** injury; here the injury is elsewhere, but is referred to the part affected.

The Different Grades of Irritation.—It was stated that the cells exposed to the most undiluted toxin are most damaged, and those farther away are less damaged, so that in the same field of inflammation there are cells reacting in different ways; it may be further said that if the same grade of toxin be applied to two cells of different orders they will react in different degrees. Thus there is found the very greatest variation in grades of response to irritation, even in the same limited area.

This question of the different resisting powers of different kinds of cells will repay closer consideration. We are able roughly to divide the cells of the body into the parenchymatous and the supporting; the former are specialized to do special work, and are exemplified by the nerve cells, liver cells, kidney cells, and so on; the latter perform more lowly functions, and are concerned in no skilled work, as it were; such tissues are the fibrous connective tissue, subcutaneous, or as the framework of organs, tendons, ligaments, fasciæ, and so on. The body may be likened to a community of which the parenchymatous cells are the professional and the skilled members, and the supportive structures the "laboring classes." In a general way, the professional classes are more highly trained, less robust, do not reproduce readily, and if one die, his place may be filled only by a person trained like himself. So it is with the parenchymatous cell in each of these particulars. On the other hand, the laborer does relatively simple work, reproduces readily, is unmoved by the ordinary turmoils of public questions, and if he die, his work is done by a neighbor who needs no special training to take his place. So it is with the supportive cell, in all these particulars. If now we have a poison of a certain intensity acting upon a parenchymatous cell and a fibrous connective-tissue cell side by side, the former is more damaged than the latter, and what is sufficient to kill the former may only irritate the latter to proliferation.

At this point we shall consider the effects of irritation on the individual cell of whatever kind. Let us suppose a toxin of very slight severity. It will at most, stimulate the cell to greater activity; if a secreting cell, to secrete; if a supportive cell, to reproduction. If now the poison

be a stronger one, it has the power of producing change in the cytoplasm of the cell:—first, the change we are accustomed to call **cloudy swelling** or **cloudy degeneration**; the cytoplasm swells, the outline of the cell may become less distinct, the plasm may appear more opaque; if the degenerative process goes farther the cell becomes granular, like ground glass, and it may show fatty, hyaline, or other degeneration (although we do not know exactly what circumstances determine one form of degeneration and what another), and finally may die. This gradual advance toward death we have designated as a bionecrescent process. If the toxin be yet stronger the cell may be instantly killed. We can thus picture to ourselves a toxin killing at once the

Fig. 26

Inflamed mesentery of frog: *a*, margination of leukocytes in the dilated capillaries; *b*, migration of leukocytes; *c*, escape of red corpuscles; *d*, accumulation of leukocytes outside the capillaries. (After Ribbert.)

cells nearest, causing the bio-necrescent process with subsequent death in those a little farther away, the same process with recovery in those yet farther away, and cloudy swelling in those still more remote, while those farthest removed, yet within the sphere of influence of the toxin, are merely irritated to activity of function, phagocytosis, chemiotaxis, or reproduction. In every composite picture of inflammation, the student must keep in mind that although we may lay stress upon other more macroscopic features, yet in each field there may be cells in all stages of "sickness."

Inflammation in a Vascular Area.—Let us consider what happens in such a tissue as the ordinary lax subcutaneous tissue, plentifully

supplied with bloodvessels. In this, let us suppose that the irritant—say a clump of bacteria—is multiplying; the toxins are being given off in all directions. The first step which is observed on the part of the tissues is that the capillaries dilate, and the stream, though larger, becomes slower; at the same time the leukocytes begin to drop out of the blood current and lag along the walls of the capillary, where presently a whole row of them is seen. These begin to progress through the capillary wall, by a flowing movement of the protoplasm— diapedesis—and soon some are to be seen outside the vessel. Serum has also been exuding at the same time, so that the connective-tissue cells come to lie well apart; many of these last are noted to be in a swollen state.

Fig. 27

1, adhesion of leukocytes to the walls of a capillary in an inflamed area; 2, mode of migration of a polynuclear leukocyte seen under higher magnification. (Lavdowsky.)

What is now going on is a struggle between bacteria and serum aided by leukocytes and sometimes by tissue cells, for if the last are not too severely injured they will proliferate, urged thereto by the irritation of the toxin. The leukocytes and the newborn cells of the part are actively "phagocyting" the bacteria, and many microbes are thus destroyed. In the meantime the blood in the capillaries is circulating, and the lymph outside of them is also, in its own slow way, circulating, so that it will readily appear that there is great activity in such an area; the area in question is now a mass of leukocytes, of cells of the part, old and newborn, soggy by reason of the excess of lymph which has exuded from the capillaries. Up to the present moment, then, we have a preliminary dilatation of vessels, margination of leukocytes, diapedesis of the same, exudation of serum, and phagocytosis. At this stage the part inflamed will show the classic signs of inflammation: **dolor, rubor, calor, tumor**; dolor, or pain, because of the irritation of the nerve endings; rubor, or redness, because of the excess of blood which is present by reason of the dilated vessels; calor, or heat, because of the increased flushing of the part by the warm blood; and tumor, or swelling, because the tissue is bulkier than it was by reason of the excess fluid, by the leukocytes newly brought in, by the tissue cells newly born, not to mention the greater bulk of blood in the vessels. This mass of leukocytes and other cells is now on the point of becoming an abscess; if, however, the resistance of the body be successful, the

bacteria become eaten up by the cells, or attacked by the lysins of the serum, and the leukocytes, which have not died, wander away again or are carried by the lymph; the excess lymph itself disappears, the bodies of the cells which have died are disintegrated, and the pieces "scavenged" or cleared away by their living fellows, and the tissue becomes as it was at first, with the exception of the proliferated cells of the part, which remain. These **fibroblasts** in time become true functioning connective-tissue cells, and the total result of the inflammation is that there is a **fibrosis**, an increase of these fibers at the spot where the inflammation existed. This constitutes the process of repair and absorption in an inflamed area.

If, however, the fight is not won by the cells but by the bacteria, let us consider what happens. We revert to the stage at which we have a soggy mass of leukocytes, new cells of the part, bacteria and serum, in fact, "the inflammatory mass." As the bacteria multiply and give off more toxins, more and more leukocytes die by reason of bacteria ingested or of toxin absorbed; especially those leukocytes and cells that are most in the centre of the mass are apt to die, because their oxygen and food supply is cut off by the dense crowd surrounding them, and their excretion is not carried away freely from them for the same reason; when they die, we find that the centre of the inflammatory mass becomes a mass of dead and living leukocytes and bacteria floating in serum—in other words, **pus**, and the whole area with its contained pus forms an **abscess**. The tissues yet alive bordering on this liquefied centre are in a case that is little better, and suppuration spreads, and the tissues bordering the abscess, as it were, melt into it until the abscess either breaks to the outside, is opened by incision, or stops by virtue of the tissue resistance.

Before we consider how such a lesion is repaired, let us glance a moment at the varying grades of cellular implication we meet. At the edge of the tissue bordering on the pus, the cells, leukocytes and tissue cells alike, are in a bad way; many are severely hit by the toxin and are dying; as we progress outward where the toxin is less strong we find cells that are severely but not fatally "sick"; farther out, cells that are perhaps in the state of cloudy or granular swelling, only slightly "sick"; whereas on the outside is a ring of cells only excited, called in by chemiotaxis, **irritated**, and these form a kind of leukocytic ring like policemen surrounding the area of disturbance to see that none of the offenders—the bacteria—escape; and, once the disturbance has subsided, to carry off the maimed or dead. **In every "inflammatory mass" we can find cells showing every grade of damage,** and generally speaking, the connective-tissue cell will suffer less than any of its fellows, parenchymatous cells or leukocytes.

The Repair of an Abscess.—If the pus be evacuated, it remains for the tissues to fill in the gap; this is done by the cells of the part; the connective-tissue cells, irritated to reproduction, bring forth fibroblasts, large, soft, vegetative cells, which heap up, taking their nourishment

from the lymph and from the slips of new capillaries that begin to
grow between them. These cells in the mass form **granulation tissue**
(in the words of the laity "proud flesh"). If the abscess be drained,
there is no great amount of severe toxin in contact with them, and they
rapidly proliferate and fill up the cavity; if the pus still remain in con-
tact with them, this acts as a permanent irritant and they are prone
to be killed by its toxins; if the wound be much washed, the washing
is apt to float them away; in either case the process of filling up is
retarded. If, however, they get a chance, the space is quickly filled up,
even overfilled by these big, soft, young cells; in the course of time these
cells become more fusiform, throw out processes which anastomose
with one another (see Fig. 31), and later give off or control the forma-
tion of fine fibrils which appear in the intercellular spaces, gradually
grow smaller, firmer, more like adult fibrous connective tissue, till finally
each fibroblast has become a connective-tissue cell, tightly bound to its
fellows, strong, and smaller in bulk than when it was younger and softer.
This is the scar; it occupies less space than did the granulation tissue
it represents, and therefore occurs the **contraction** which characterizes
the scar; it is dense, and this accounts for its hardness and unyielding
character; it is also relatively bloodless, through pressure upon the
previously abundant capillaries. If the pus has not been evacuated,
it remains as a kind of foreign body; its serum drains away, and from
being liquid it becomes of the consistence of butter, then of the con-
sistence of cheese, and finally, dry or inspissated. Meantime, the
surrounding tissue has been forming granulation tissue about it, and
this granulation tissue becomes in time scar tissue, and the scar instead
of filling up the gap where the original loss of tissue occurred, sur-
rounds the dried-up pus, as with a wall. The remains of the pus in
time frequently become permeated by calcareous material deposited
from the lymph, so that such an abscess may be finally represented
by a mass of calcification, surrounded by a wall of fibrosis.

The various changes noted in an inflamed area call for a more
precise description than we have given, and some particulars may
be outlined.

Circulatory Changes.—With the advent of the irritation, the vessels
momentarily contract, and then dilate; and yet at the same time the
flow of blood is not quicker, but rather slower, and the serum of the
blood flowing out of the part is more abundant and contains a higher
percentage of solids than is ordinarily found. The change in calibre
of the vessels is not due to the influence of the central nervous system,
but is probably brought about by some local effect on the vessel walls.
The margination of the leukocytes is not so much an active quality of
the leukocytes themselves as caused by a change in the endothelium
of the capillaries, by which it gains an agglutinative quality.

The exudation of serum is not merely an accompaniment of the
dilatation of the vessels but is an indication of some change in the endo-
thelium; the exuded serum is more bacteriolytic than normal blood

serum, although most of this quality is gained at the site of inflammation, where it picks up proteolytic, antitoxic, and bactericidal substances, the products direct and indirect of cell dissolution, especially of leukocytes.

In all the preceding paragraphs we have said nothing about fibrin formation, which is so obvious an accompaniment of inflammation on a serous or a mucous surface. Yet even in deep tissues it may exist. The serum supplies fibrinogen, the leukocytes fibrin ferment, the body fluids the necessary calcium in the medium, and fibrin is deposited in the tissue, where ordinarily its existence is but a short one, because of the presence of proteolytic ferments which, readily produced by the pyogenic organisms, quickly dissolve it.

The Endothelium of the Bloodvessels.—We have indicated that the endothelial cells lining the bloodvessels and constituting the walls of the capillaries are not "tiles" laid in, as in a mosaic, but are active cells joined to one another. They can expand and contract, they can govern to some extent the quality of fluid passing between and through them; they have even been seen to send out pseudopodia and seize bacteria in contact with them, and they are active phagocytes. It is possible, though not proved, that the large mononuclear cells of the blood are the progeny of these endothelial cells. When the capillary is contracted, the spaces between them are small, but when the vessel is dilated, they are large, and it is through these spaces that diapedesis of leukocytes occurs; it may happen that red-blood cells are pushed out through these large openings, especially those which have been stretched by the previous passage of a leukocyte; but the existence of red-blood cells outside the vessels in an area of inflammation is no essential part of the process.

Closely related to these endothelial cells are the endothelial cells lining lymph spaces and the body cavities. These are capable of reproduction; and the cells that we see born from them are large, acidophilic, hyaline cells that are actively phagocytic. These cells we find lying amid the tissue cells, and they are of the same order as the large hyaline cells given off by a serous surface. The fibrous connective-tissue cell which we picture as the basis of supportive tissue is actually lining a potential lymph space; and the cells that we recognize as lining lymph channels and lymph sinuses are the same kind of cell; the capillary endothelial cell is the same cell directing the flow of blood instead of lymph, and the serous surface cell is once more the same cell with a special function of protection. Therefore, it matters not whether the progeny of these ·cells be set free in the blood stream, the lymph stream, the tissue spaces, or the serous cavities, for they, the progeny, are like cells, playing a like part in protecting the body during inflammation. This part is to perform phagocytosis, and, as fibroblasts, to be the cells that will fill up the gaps that have occurred in the tissue, and ultimately to be the cells of the scar. This, it is but right to the reader to mention, is

regarded by some as heretical doctrine: not a few pathologists hold to the view that the cell of endothelial origin and the fibroblast, the derivative of the connective-tissue cell proper, are distinct cell species. This we admit as regards their origin: we fail to see that in inflammatory tissue they are distinguishable in their vegetative states or their ultimate fate: both may become fully formed fibroblasts and give origin to scar tissue.

FIG. 28
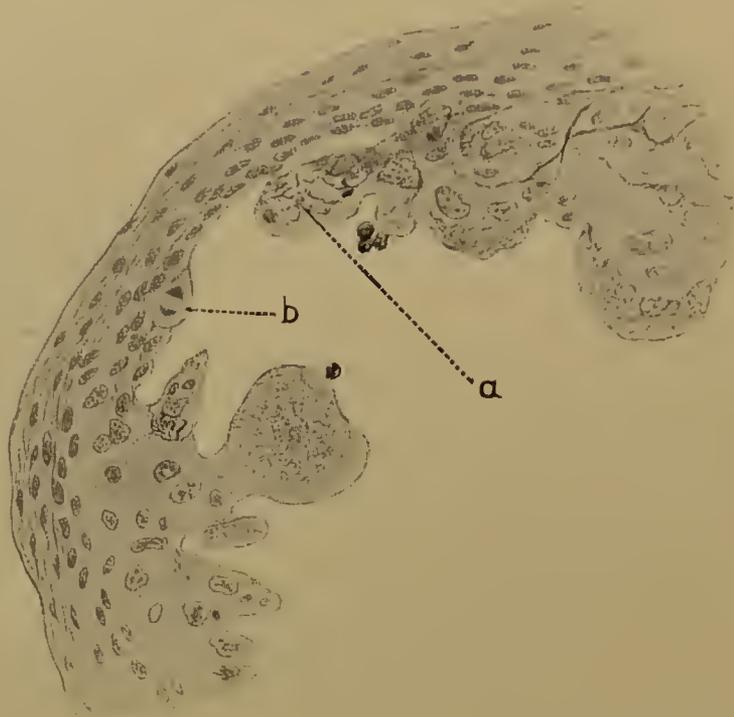
Wall of small artery with proliferating endothelium: *a,* phagocytic endothelial cells; *b,* attached endothelial cell undergoing mitosis.   (Duval.)

The Blood Cells.—The leukocytes are called to the part that is inflamed by the process of chemiotaxis.   This implies that there is a passage of fluid not only from the vessels to the tissues, but from the tissues to the vessels, and the leukocytes are impelled to the part where certain substances are in greater or less concentration; it implies, too, a considerable diffusion of the toxins from the spot where they are manufactured.   We do not mean to say that a call reaches the leukocyte in a distant part of the body, but we do think that of the leukocytes that pass by way of the inflamed area the greater number are held, caught by the agglutinative quality of the endothelium, and remain to assist.

The leukocytes that take part are the polynuclear (properly polymorphonuclear) cells, the lymphocytes, and the eosinophiles.   The first of these, the **polynuclear,** with a horseshoe-shaped or, more commonly, a partite nucleus, are the most common in the affected area in a case of acute inflammation; they are active phagocytes, liberate during disintegration, possibly in life and certainly in death, antitoxic, proteolytic, and bactericidal substances, move away into the lymph

PLATE IV
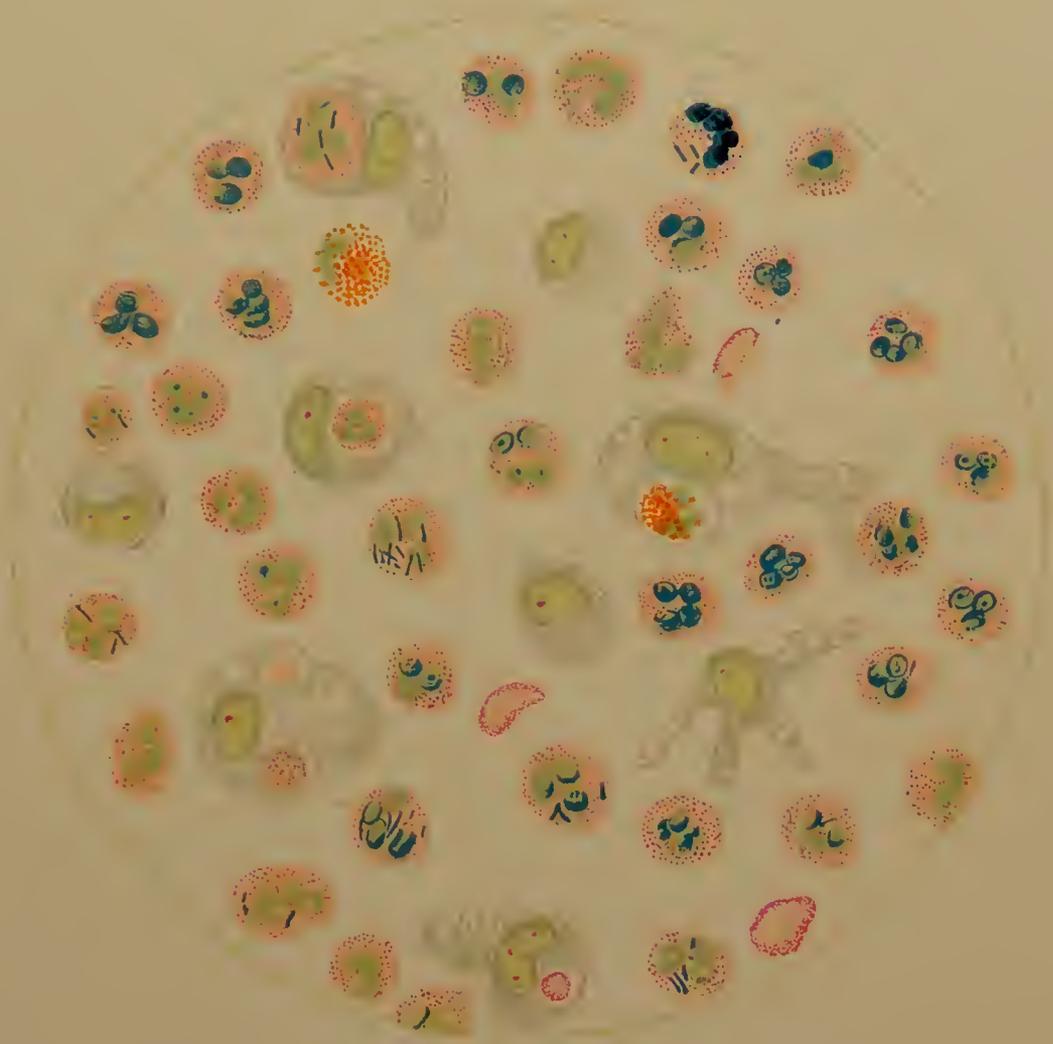
Wandering Cells in the Peritoneal Fluid of a Rabbit Twenty-
four Hours after Injection of B. coli into the Peritoneal
Cavity. (Beattie.)

To show the relative proportion of polynuclear and eosinophile leuko-
cytes to the mononuclear (histogenous or hyaline) leukocytes. There is
already some phagocytosis, polynuclears, eosinophiles, red corpuscles by
the mononuclears, along with bacillary phagocytosis by the polynuclears.

stream again or remain to be eaten whole or in pieces by the endothelial cells, and take no part in tissue formation. These originate most frequently from the bone marrow, although sometimes from the spleen, liver, and hemolymph nodes. The **lymphocyte** plays a much more subordinate part in acute inflammation, though an important part in later stages and in more chronic disturbances; weakly amœboid and weakly phagocytic, it yet has been seen to wander through the vessel wall, and to ingest particles, but not the bacteria of suppuration. The lymphocyte can give rise to the plasma cell, of which more anon.

FIG. 29
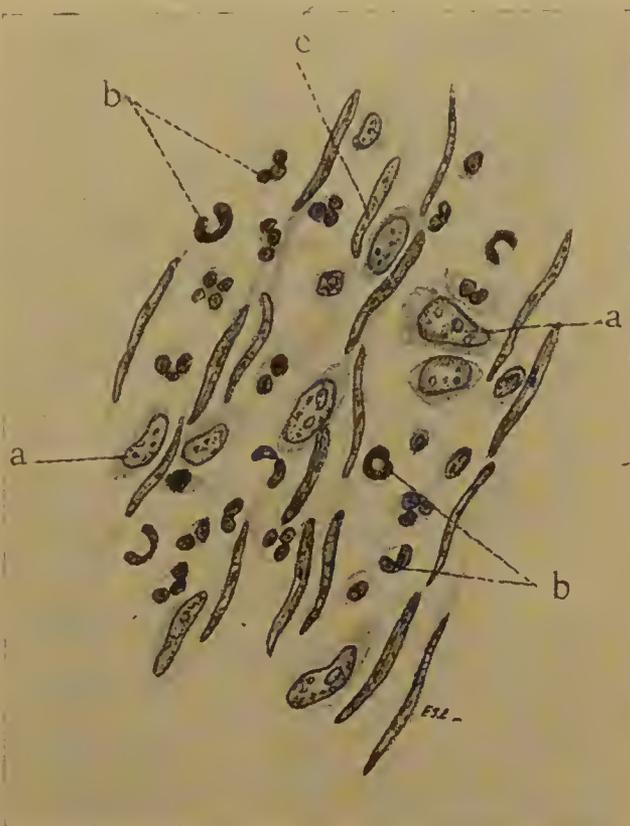
Polynuclear leukocytes infiltrating the circular muscle layer of an acutely inflamed appendix: *a, a,* endothelial cells; *b, b,* polynuclear leukocytes; *c,* nucleus of muscle cell.

The important point to note is that while in a very acute inflammation, the result of virulent toxin, they are rare, in a 'ow grade inflammation, caused by a less active toxin, they are common. So much is this the fact, that in a serous-sac inflammation we are in the habit of counting the cells in the exudate, and of concluding that a large percentage of lymphocytes speaks for an inflammation of second-grade intensity like tuberculosis, and not for one of first-grade virulence like that set up by the pyogenic organisms. The lymphocyte originates in greatest abundance from the lymph nodes; it has, however, to be kept in mind that in the sheaths of most veins there is normally present a zone of lymphocytes, and that those which accumulate in an area of inflammation are not necessarily all derived from the blood, but

some at least are the result of proliferation of these local lymphocytes. The **eosinophiles** we cannot yet rank in their proper place; they have the same power of migration as the ordinary leukocytes, less power of phagocytosis, and appear early in some acute inflammations. Like the polynuclears they originate mainly in the bone marrow and they have no part in the formation of new tissue. We may say here that no cell with multiple nuclei or a partite nucleus does enter into tissue building; these cells, as we stated before, are marked for an early death, and are already on the downward road.[1]

FIG. 30

Acute lymphadenitis, showing a lymph sinus containing (*a*) large endothelial cells, some breaking down, others (*c*) acting as phagocytes. To the left are numerous lymphocytes (*b*) for comparison.

The Fixed Tissues.—These play a very important part in inflammation, despite the fact that their cells are less prominent than the leukocytes; if the irritant be one of slight degree, proliferation of the stroma cells appears from the first; if of high degree, the stroma cells at the centre of activity may be killed, but those in the surrounding areas are excited to phagocytosis and to proliferation, and the degree of toxin that is able to kill a leukocyte is probably not able to kill a stroma cell, or a fibrous connective-tissue cell as we have called it previously. In the area of inflammation, and appearing there as a result of the process, we find three sorts of cell, which we will describe one by one: (1)

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[1] The fullest recent work upon the blood cells is that of Gruner. The book is highly technical, but no other work in our language gives so fully the latest results of hematological observation, more especially of Pappenheim and his school and its portentous nomenclature.

PLATE V

FIG. 1

Wandering Cells from the Peritoneal Fluid of a Rabbit
Thirty-six Hours after Intraperitoneal Injection of B. coli.
(Beattie.)

To show large phagocytic mononuclear cells ingesting polynuclear leuko-
cytes, red corpuscles, and bacteria.

FIG. 2
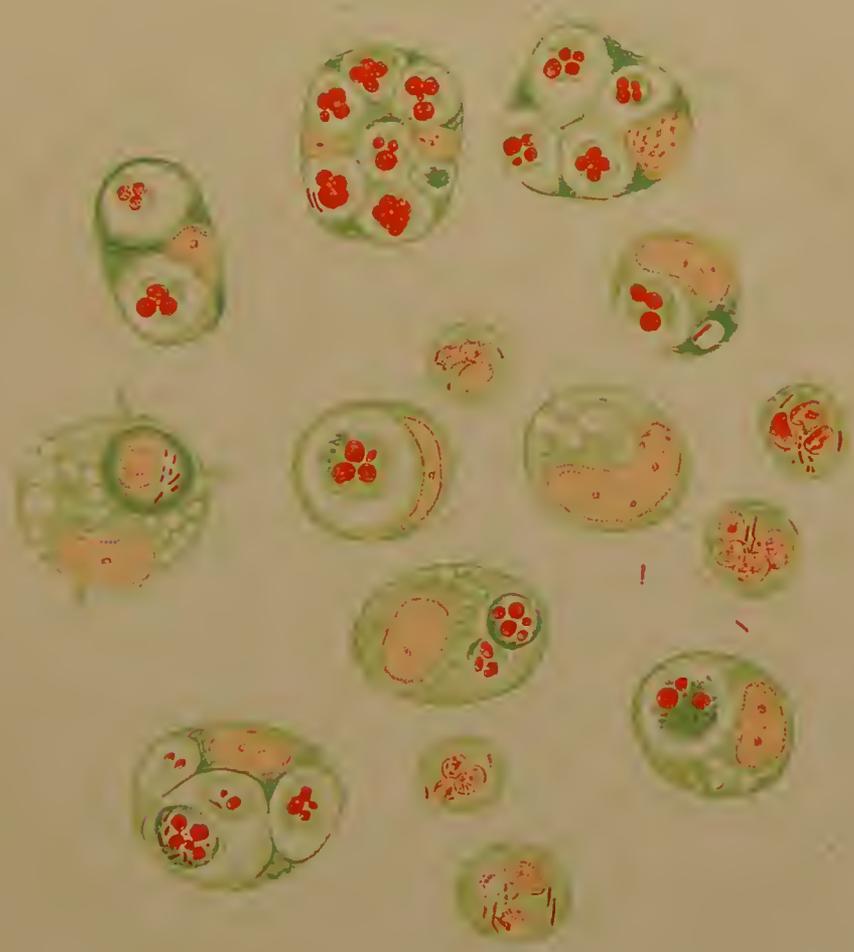
Wandering Cells (Mononuclear, Hyaline, Histogenous) from
the Peritoneal Fluid Forty-eight Hours after Intra-
peritoneal Injection of B. coli. (Beattie.)

To show phagocytosis and digestion of polynuclear leukocytes and
digestive vacuoles. (Later stage.)

The endothelial or hyaline, mononuclear leukocyte (see Fig. 30), a relatively large cell, non-granular, actively phagocytic for erythrocytes and other cells, which is like the cell appearing in the blood, which, too, we have stated above to originate, in all probability, from the tissues; (2) **the fibroblasts** proper, oval, becoming spindle-shaped, originating from the fibrous connective-tissue cells, and (3) the so-called **plasma cells.**

FIG. 31
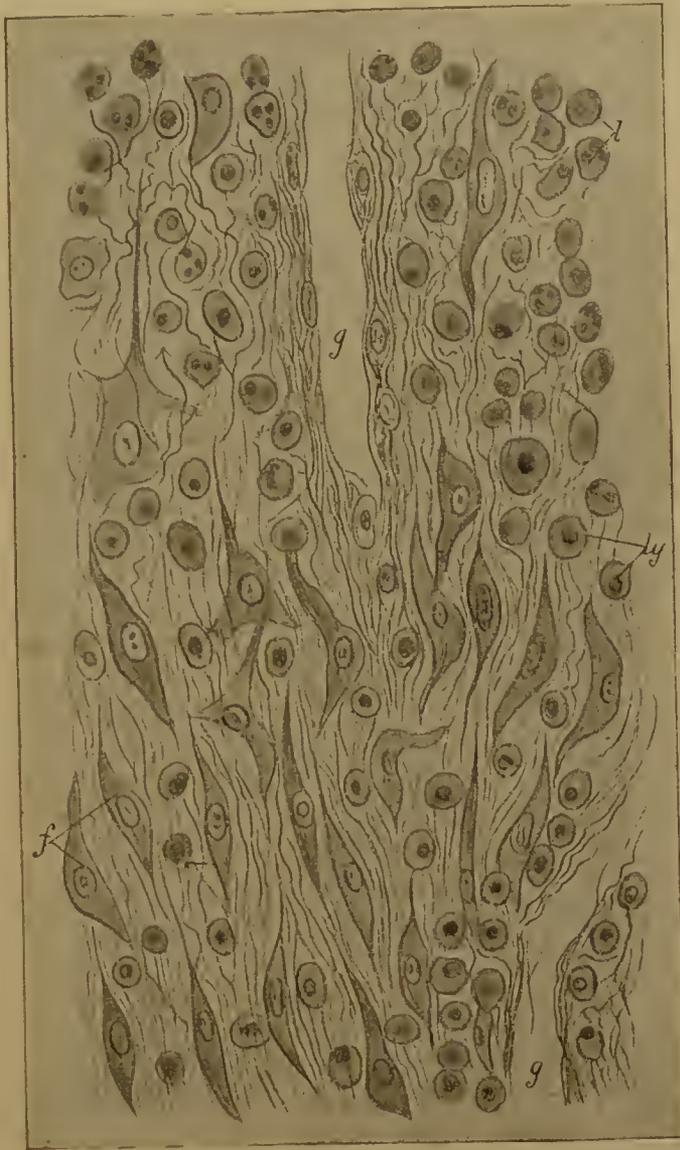
Granulation tissue seen from the deeper toward the upper surface: *f*, spindle cells (fibroblasts), most abundant in deeper portions, where they also are becoming shrunken; *ly*, lymphocytes; *g*, capillaries. (Ribbert.)

The Endothelial Cells.—These are especially numerous on inflamed serous surfaces, and are definitely known to arise from the endothelium of those surfaces; some observers studying other areas of the body consider that they come from the lymphocytes, but this we are inclined to doubt. Their functions of phagocytosis we have already mentioned and they appear to enter into connection with the surrounding cells and to build up new tissue. As already noted we

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are not convinced that all these cells originate from lymphatic endothelium: in the inflamed lymph node, for example, they appear to originate also from the cells of the reticulum, and in the early tubercles we find it difficult to believe that all the epithelioid cells are of endothelial source, and not, in part at least, proliferated connective-tissue cells. With these reservations we accept the term "endothelial" which today is gaining vogue, regarding it as useful to the extent that it indicates that these are of local tissue development.

The Fibroblasts.—These are born as large, round cells becoming oval, and in time they form fine fibrillary connections with the cells nearby, become spindle-shaped, and ultimately form connective-tissue cells such as their parents were.

Fig. 32

From a case of subacute colitis, demonstrating abundant plasma cells (*b, c, d*) surrounding a degenerating follicle of Lieberkühn (*a*) in which the columnar cells have become detached from the basement membrane.

Plasma Cells.—We here approach a topic still causing considerable confusion. An important group of observers regards the plasma cell as of lymphocytic origin. It is a cell, found in the tissues in cases of subacute rather than of acute inflammation, rounded or polygonal in shape (Fig. 32) with eccentric nucleus and basophile cytoplasm, often exhibiting a clearer space or zone at one side of or around the nucleus. Once recognized it is quite characteristic. It shows little or no phagocytic powers, nor, according to these observers, does it play any part in the development of fibroblasts. These considerations coupled with its frequent presence, not to say abundance, in cases of inflammation of moderate grade have led observers to promulgate that it acts by affording an excretion.

On the other hand, Maximow, a very capable observer, has a

PLATE VI

Granulation Tissue. The Upper is toward the Outer Surface.
(Maximow.)

end., capillary endothelium; *new cap.*, endothelium of newly forming capillary; *fbl.*, fibroblasts; *l.*, polynuclear leukocytes; *x.*, the polyblasts of Maximow (including plasma cells); *deb.*, debris of leukocytes; *deg.*, a degenerating "polyblast."

considerable following in support of the view that the plasma cell is but one phase in the life history of what he terms the "**polyblast**," a cell that is, which may originate either from lymphocytes or connective-tissue cells, which may develop into fibroblasts and so into connective tissue, or into **clasmatocytes**, large cells with pronounced processes, which are constantly shed, into "**mast cells**" of the tissues, or cells filled with large basophile granules or into cells of the above-described plasma-cell type. The matter is still under debate.

FIG. 33
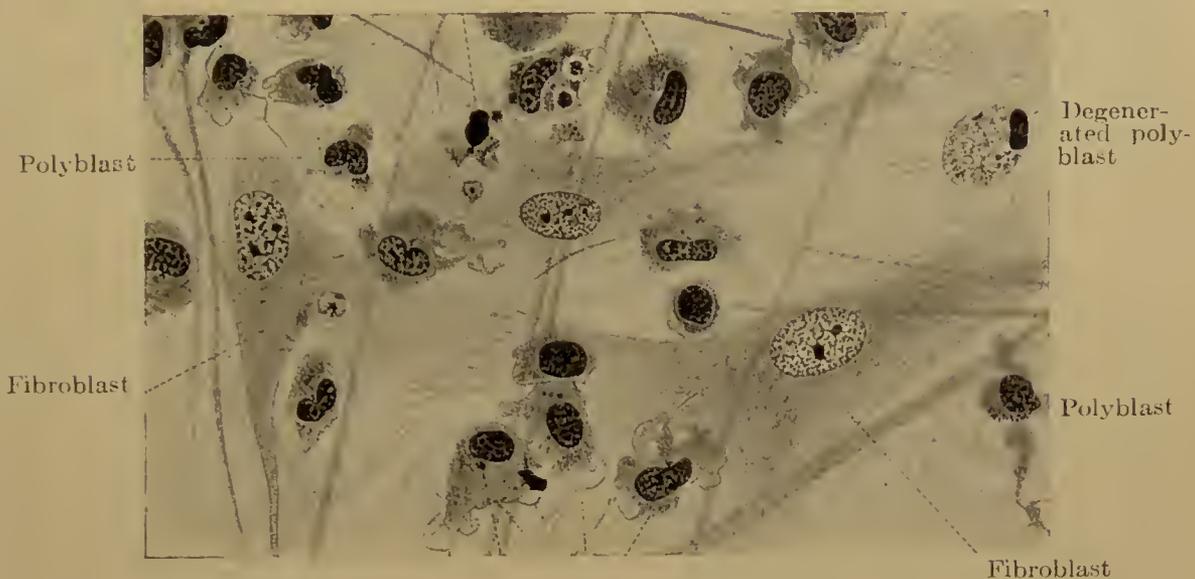
Developing connective tissue.   (Maximow.)

Inflammation of a Mucous Surface.—In putting together the details which characterize an inflammation of a mucous surface we have to consider not only the surface itself, but also the tissues that underlie it for a short distance, because these also are attacked by the irritant. In them the process is that which we have just described. In the milder conditions what we observe is a swelling and active proliferation of the epithelial cells of the mucous surface, and the production both by these cells and by the small mucous glands of the part, of abundant mucin. There is thus produced a surface discharge of serous fluid mixed with abundant mucin, loosened columnar cells, some few leukocytes, and where these are more abundant, there may be present in this discharge scattered threads of fibrin. This is what is termed **catarrhal** inflammation. Where the irritation is more extreme, there the columnar epithelium of the part may be completely cast off, and with this the character of the exudate is changed from a mucinous to a more serous one with abundant leukocytes, and with the formation and deposit of fibrin this forms a moist layer of interlaced fibrils that entangle in their midst leukocytes, often bacteria, while the interstices are full of serum. Add to this, there are generally superficial cells that, attacked by the toxin, damaged or killed, have become separated and

now lie in the **exudate**, for such is the name applied to the material, solid and fluid, which is given off by the surface. If the exudate contain much fibrin and lie upon the surface, its tough consistence has given to it the name of a **membrane**.

We are accustomed to use many adjectives in describing an inflammation of a mucous surface, designating it by that term which expresses its most striking feature. Thus, if there be plentiful clear secretion, we call it serous or catarrhal; if the leukocytes be relatively numerous in proportion to the amount of fluid, so that the latter is slightly opaque, we use the term **seropurulent** or **mucopurulent**; if the leukocytes are so numerous that the fluid is yellow or white, we call it **purulent**; if there be much fibrin, **fibrinous**; if less, but still an appreciable quantity, **serofibrinous**; if there is much fibrin and also pus, **fibrinopurulent**; if a membrane appears, **membranous**; if the surface sloughs away, **necrotic** or **ulcerative**; if abscesses under the surface do not burst, or until such time as they do burst, **phlegmonous**; if bloodvessels be ruptured, either on the surface or under it, **hemorrhagic**. It will appear that there are many modifications of the same process; if one judged merely by the salient feature, one might think that we had to deal with many different kinds of disease, yet in each case the same march of events is happening, with the difference that in one it is this character which predominates, in the other that. Let us designate each feature in the process by a letter—thus, let *a* represent the hyperemia; *b*, the exudation of serum; *c*, the diapedesis of leukocytes; *d*, the proliferation of the cells of the part; *e*, the formation of fibrin, and so on. Each case of inflammation is represented by *a, b, c, d, e, f*, etc. If, now, we represent each salient characteristic by the heavy type, we find a particular case represented thus: *a, b,* **C**, *d, e, f,* or **A**, *b, c, d, e, f,* or *a, b, c, d, e,* **F**. Looked at carelessly or from a distance, it might seem as if these were different cases, the salient feature only being distinguished; but looked at closely, all are at bottom the same familiar process. Thus it has come about that we speak of so many apparently different forms of inflammation; the truth is that the tissues are not educated to distinguish different irritants, and respond to all in precisely the same manner, showing differences of *degree* but none of *kind*.

Inflammation of a Non-vascular Area.—The non-vascular areas of importance are cartilage, the lens, the cornea, and the outer half or two-thirds of the cusps of the heart valves. Of these the cornea affords the most favorable region for study of the process. Here, in the slighter grades of inflammation, the main change seen is a swelling with subsequent proliferation of the corneal corpuscles. The leukocytes are necessarily few in number because only the lymph has access to the tissues; while few, it can be seen that these gather, attracted by chemiotaxis, in and around the injured area. In severer grades of irritation, such as can be produced experimentally by inoculating into the cornea with a fine needle a small amount of pure culture of one of the pyogenic organisms, successive stages may be made out. As in the course of a

few hours the inoculated microbes begin to proliferate, it can be observed that the surrounding corneal corpuscles become distinctly swollen and show evidences of degeneration. With this there is a similar accumulation of leukocytes out of the surrounding lymph spaces toward the focus of irritation. In a few hours more, the circular vessels at the periphery of the cornea become dilated, and with this there sets in a migration of leukocytes from the vein. While this is proceeding the corneal corpuscles in the immediate area of bacterial growth break down, and the proliferating bacteria infiltrate over a larger area until such time as the accumulation of leukocytes from all sides forms a barrier arresting their further escape. From this point on, the inflammation is similar to that seen in a vascular area with this notable exception, that obviously the chemiotactic influence which led to the migration of the leukocytes, exerts itself also upon the wall of the circular vein, so that now buds or processes pass inward toward the affected area and then become developed into true capillaries, which may persist weeks and months after the acute inflammation has subsided.

In the heart valves a process similar to that in the cornea is seen; the area here is exposed to the double insult of a toxic or bacterial irritation, and seventy-two blows per minute, so that ulceration is likely to ensue. On this is laid down fibrin and in it leukocytes, for in addition interaction ensues between the ulcerated surface and the blood which bathes it. There are thus produced fibrinous **vegetations,** and the fibrin, in the course of repair, is replaced by fibrous tissue. In those cases in which the irritant is not very powerful, it seems that there is a proliferation of the connective tissue of the valve, without anything else, so that a heap of new fibrosis arises from the edge of the valve, and constitutes a vegetation of a fibrous kind from the very outset.[1]

Chronic Inflammation.—From the way we have insisted upon the uniformity of the process of inflammation so far, it may be inferred that we are not in favor of building up a barrier between so-called acute and so-called chronic inflammations; and such is the case. Are we to call an inflammation acute if it reaches its height in one, two, three, or four days, and chronic if it takes five or ten or fifteen? We do so, but it will be seen that the distinction is arbitrary. Or, if we are in doubt, as clinicians, whether an inflammation is acute or chronic, are we to compromise and call it subacute? As clinicians, yes. But from the pathological standpoint, it is unnecessary, because in all we see the same mode of reaction, *a, b, c, d, e, f,* as we have said above. If the irritant be of low degree of strength, there will be less killing of tissue and more proliferation, if of high degree, more killing and less proliferation, more serum, it may be, and less diapedesis, but in every case the procedure *a, b, c, d, e, f,* runs through all, as the theme runs in a piece of music all but hidden under variations.

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[1] A frequent mistake of the student is to confuse *fibrous* and *fibrinous*. The term *fibrinous* can be employed only to designate the result of deposition of fibrin.

The salient feature of an inflammation caused by an intense irritant is exudation; diapedesis occurs but little, because chemiotaxis is negative, and the leukocytes, wise in their day, remain away; proliferation can occur only at the outskirts, where the toxin is well diluted; at the centre, even the strongest cells are killed. The striking feature of an inflammation caused by a gentle irritant (such an one as we often clinically call **chronic**) is proliferation, because there is a minimum of killing of cells, of irritation such as calls forth abundant exudation and diapedesis. Between these two extremes occur many grades.

But there remains a frequently made error to correct. Too often we speak of adhesions between the layers of the pericardium as chronic pericarditis *instead of correctly calling it the results of a past pericarditis.* Pleural adhesions, nine times out of ten, do not indicate a **chronic pleuritis**, that is, a disease yet active, but indicate merely the repair of a disease active long ago and now healed, as far as may be. Yet adhesion might be slowly set up by a mild process of irritation, and such would be correctly enough called chronic pleuritis, but this occurs rarely in comparison to the rapidly produced pleuritis. Another similar mistake is to speak of a heart as the victim of chronic fibroid myocarditis, when we should say a heart with fibroses which have resulted from old myocarditis. The terminology matters comparatively little, if it be understood that the process is essentially a uniform one; the student should take heart from the consideration of the simplicity of the inflammatory process; if he understand the invariable reaction of the tissues he will see it in every case of the disease, even if it be for the moment concealed by the predominance of some one feature.

The Vascularization of New-formed Connective Tissue.—In addition to the proliferation of the cells of the part, that is, the formation of fibroblasts and, it may be, of plasma cells, and large hyaline cells, it must be recalled that the vessels play an active part in the later reparative stages of an inflammation and this particularly where there has been active destruction of tissue. In all such cases what is termed **granulation tissue** is formed. This name is taken from the appearance of a healing superficial wound, the granulation being due to the presence of closely set new capillary loops. On such an inflamed surface at first is merely a layer of leukocytes with, it may be, a few fibroblasts and large hyaline cells, but immediately beneath these it can be made out that the dilated superficial capillaries show tiny buds or thickenings of their endothelium directed toward the surface, and presently these "buds" elongate, sending processes outward, which processes from adjacent capillaries join, become more prominent, become thicker, are hollowed by the blood stream and rapidly assume all the characters of a new capillary. From these new loops other loops are formed, advancing into the area which is to be filled up, until this area is filled with a framework of new vessels, which are supported and separated by the tissue cells which have continued to be simultaneously proliferated in the meshes of this framework. This constitutes *granulation tissue,*

or, on a surface, what the layman terms "proud flesh." Only those who have watched a large deep wound heal in a healthy, growing child can appreciate the truth of the adage, "There is in the tissues an almost insuperable tendency to heal." The physician may succeed in overcoming this tendency if he be meddlesome and foolish. If there be a granulating surface, remember that antiseptics will succeed in killing

Fig. 34

Formation of new vessels in granulation tissue: 1, from a Ziegler-chamber (formed of two cover-slips) left in the peritoneal cavity of a rabbit for forty-eight days; portion of field bounded by two fully formed new capillaries; between them can be seen the solid buds and processes of developing new capillaries; 2, from a similar preparation to show formative cells, or fibroblasts, in direct connection with the endothelial processes. (Ziegler.)

these tender, newborn cells, that a stream of water may wash them away, and nature may have to do her work over again on your account. If you see pus on the surface give it a chance to drain away if possible, but remember that granulation tissue presents a very strong barrier to absorption, and the pus may do less harm than the clumsy sponge that removes it. The pus from a granulating wound was called by our forefathers, who understood the drainage of wounds as well as we do,

"laudable pus"; and when you speak of "exuberant granulation" do not without thought run for the silver-nitrate stick; granulations cannot help being exuberant.

The Infective Granulomas. — The infective granulomas are the local effects wrought by certain protozoa, certain bacteria or other forms of plant life, such as the B. tuberculosis, B. lepræ, B. mallei, actinomyces, blastomyces, Treponema pallidum, and even the larvæ and eggs of certain parasitic worms; the tissues build up a wall around the irritant, so to speak, and this mass of new-formed tissue we call the tubercle, the gumma, or the nodule, as the case may be. It is evident at once that the process of formation of such a "lump" is a conservative one, and tuberculosis, the disease, does not so much consist of the presence of the tubercle as of the destruction of the tubercle or other tissues by the bacilli and their products.

A word as to the classification of these diseases is in place. Long ago it was realized that the result of the irritant of tuberculosis was a "lump," the tubercle; this was aforetime called a tumor, and was classed among tumors; when it was found to be of fibrous tissue, *i. e.*, of granulation tissue, it was called a "tumor of granulation tissue," or a **granuloma**, using the termination—*oma* which we have made to signify the idea of a tumor. When it was discovered that the B. tuberculosis was the cause of this granuloma, it was designated an "infective granuloma." Thus, one by one, the class has grown, as each infective agent has been discovered; and now we are able to state that the process is purely an inflammatory one, and that the granuloma is merely the lump that results from the proliferation of the cells of the part in response to the toxin of the organism concerned. In fact, all that has been said of the "inflammatory area" above is true for the formation of the granuloma, although the process is a longer one in time; the toxin of the B. tuberculosis causes a dilatation of the bloodvessels, a moderate exudation of serum, a slight diapedesis of leukocytes, and a great proliferation of cells of the part—the so-called *epithelioid cells*, which term we mention only to reject; they should be called the **endothelial** cells or the **proliferated cells of the part**; while the centre of an acute inflammatory area, rich in serum and badly damaged by toxin, breaks down rapidly into pus and an abscess is formed, the centre of the granuloma breaks down slowly into a formless mass of dry necrosis—caseation—and a caseated granuloma is the result. Tuberculosis is, clinically, a chronic or at times, a subacute inflammation. Another point of parallelism between these agents and those causing acute inflammation is this: if tubercle bacilli are in sufficient numbers they can excite an acute inflammation not to be distinguished from the results of the pyogenic bacteria. The same has been shown to be true of the glanders bacillus, while in man, the nodule of actinomycosis has very commonly a central area with abundant polynuclear leukocytes; in fact, contains true pus, while around this is a zone of proliferated tissue cells.

The tubercle, the gumma, or the nodule, thus, is a mass of new-formed connective-tissue cells, and these cells are the essential part of the tubercle; the trained microscopist must become used to recognize the granuloma by this; the giant cell, of which more anon, is unessential; the caseation is an unessential, save that if sufficient time be given it is an almost inevitable sequel, at least in cases of tuberculosis; the ring of leukocytes external to the mass is also unessential, although the more acute the process the more likely it is to be present; the proliferated tissue forming the "lump," the tubercle, the gumma, the nodule is the essential, and the only essential. And in most cases of these maladies the unit is the granuloma, and a cavitated lung is merely the final result of necrosis, secondary infection and what not on an aggregation of small granulomas.

FIG. 35

Tubercle from a case of tuberculosis of medium severity of the lung: *a*, central caseation; *b*, a giant cell; *c*, endothelial cells; *d*, connective-tissue zone infiltrated with lymphocytes.

Giant Cells.—Although not a necessary character of a tubercle, the giant cell is very frequently found therein; this is characterized by a large body, made up of ill-staining, acidophilic, necrotic material, with a crescent, a ring, or a group of ordinarily stained nuclei; this is sometimes clearly the result of fusion of a group of cells to form a plasmodium around a small mass of necrotic material or of bacilli—in other cases there are indications of actual nuclear multiplication with incomplete cytoplasmic division. The giant cell is often found close to the necrotic part of the tubercle, and in this edge, or in the giant cells themselves, the bacilli are to be most readily found. Interspersed, too, with the proliferated cells of the part are lymphocytes and rarely leukocytes— the former are the "small, round cells" of inflammation—and on the outside is a more or less pronounced ring of lymphocytes which have been attracted to the area of inflammation by chemiotaxis.

Here it may be useful to recall that the presence of the giant cell is by no means limited to tuberculosis: we encounter similar giant cells in other infective granulomas, in syphilis, actinomycosis, blastomycosis, and glanders. A somewhat similar type of cell is seen filled with the lepra bacilli in leprosy. Wherever foreign bodies occur in the tissue, as shown in Figs. 25 and 36, plasmodial giant cells may be encountered. Another type is seen in the osteoclasts of normal bone, and apparently similar to this are the giant cells of myeloid or giant-celled sarcoma. Yet other multinucleated giant cells are not infrequent in other forms of sarcoma, while in certain cases of Hodgkin's disease we may encounter relatively huge cells which are truly giant cells, but have only one or two nuclei.

FIG. 36

Giant cell or cells from a case of inflammation of the subcutaneous tissue: *a, a*, cells of endothelial type; *b, b*, the same in process of fusion into the mass. (Dr. Rhea.)

Diffuse Inflammation.—Sometimes the organisms of the infective granulomas do not set up the localized nodule, but we find a diffuse fibrosis such as happens in the pia mater in syphilis; nor is this confined to the group of organisms which cause the granulomas, for a good example exists in cirrhosis of the liver, where there is a general increase in the connective tissue of the part without there being any particular localization. It may be, however, that this diffuse fibrosis is an after result of the existence of small multiple granulomas. At times it appears to be caused rather by the toxins of the organism than by the organisms themselves. Such a fibrosis—a **cirrhosis**—is common in the liver in syphilis, as well as in cases where a long-continued exposure of the liver to the bacterial and other toxins of the alimentary tract leads to the fibrosis which is known as "cirrhosis of the liver." There is a further class of cases which we term "chronic inflammation," which arise in a way similar to this. Such are chronic nephritis, thyroiditis, and hepatitis, all of which we recognize as caused by an

irritant, yet in which we think faulty metabolism and imperfect nutrition are also of some effect. It is supposed that under the influence of disturbed or excessive activity the secretory cells become degenerated and die, the fibrous tissue filling up the space left by them; the two processes just referred to occur simultaneously, the same irritant causing degeneration of the higher-class cells and proliferation of the lower-class supportive cells.

Fig. 37
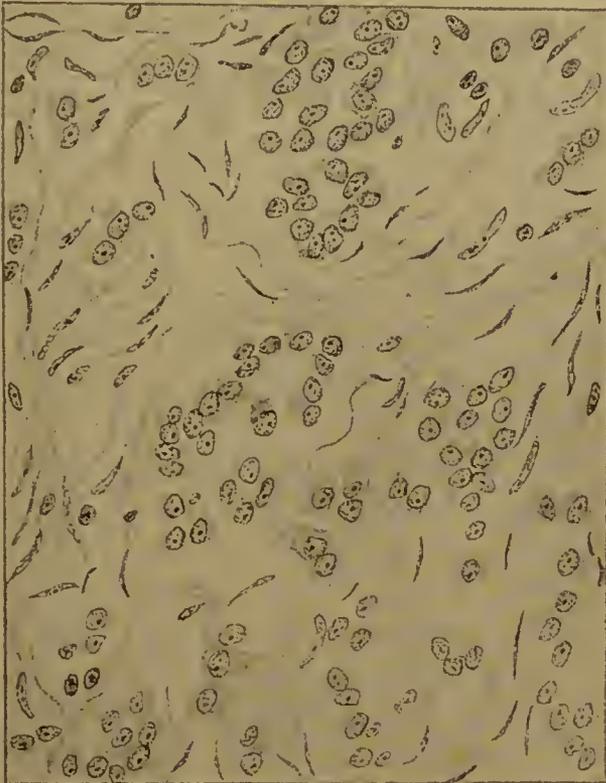
Section from a syphilitic liver which presented gummata along with extensive cirrhosis. The new-formed connective tissue is seen extending between and cutting off islands of liver cells, which as a result are shrunken and atrophied.

Fibrosis and Inflammation.—So frequently has the proliferation of connective tissue been dealt with in connection with inflammation, that the question arises, " Is fibrosis always the result of inflammation?" The answer is in the negative; the formation of a fibroma or a new growth is, of course, a case in point; the occurrence of fibromatosis, of elephantiasis, of macroglossia all indicate the readiness with which fibrosis occurs if there be an obstruction to the exit of the lymph by its ordinary channels. The obstruction of the lymph prevents the free drainage away of the toxins of the cells, which toxins, remaining, may excite the fibrosis; this becomes thereby a case of inflammation; although, on the other hand, with the absence of obstruction of the veins there may be free diffusion away of any such toxins, and the process may be regarded as a result of stress, to be presently mentioned. Finally, there is the difficult problem that is presented by fibrosis of the intima of a bloodvessel in arteriosclerosis. Here we find two forms: in one, the intima is primarily the site of change,

and this we may attribute to irritation, but the others are adaptive, to strengthen the wall at a place where the media has degenerated; such fibrosis occurs without any leukocytic infiltration or formation of new vessels, and may be partly explained by what we have not previously adduced as a cause of proliferation, namely, stress. If cells are put upon a constant not excessive stretch, or even are intermittently exposed to such a stress, if they be well nourished, proliferation ensues, the distension acting as a stimulant. Here we have no injury; it is too great a stretch of the imagination to consider this as an inflammation.

We feel that this is a principle of wider application than is generally appreciated, the principle, namely, that mechanical force exerted either as pressure or traction upon a cell, is able to cause the growth and proliferation of that cell, so long as, at the same time, there is no interference with its nutrition, and the force acting on the cell is not excessive. Overstress or diminished nutrition will lead to the opposite condition of atrophy. What applies to the cell individually applies to cells in the mass; thus, as a matter of experience, it is found that the constant pulling of a tendon upon a bony ridge is followed by increase in the size of that ridge, *i. e.,* increased bony growth.

We may thus classify the fibroses:

I. OF INFLAMMATORY ORIGIN.

1. *Replacement fibrosis,* in which the fibrous tissue takes the place of other tissue that has been destroyed. The "scleroses" of the nervous system, arising from glia, are here to be included, as well as in part the fibrosis of "nephritis" and "hepatitis."

2. *Proliferative fibroses,* such as (*a*) the fibroses of the granulomata, and those around foreign, inert bodies, and (*b*) post-inflammatory fibroses in which the fibrous tissue continues to grow even after the irritant has ceased to act, as in **keloid.**

3. *Post-fibrinous fibroses,* which replace fibrin in a thrombosed blood vessel or on a serous surface (adhesions); these partake of the nature of both the above groups. They are replacement fibroses in that they replace the fibrin, and proliferative in that they occur where previously no tissue proper existed.

II. OF NON-INFLAMMATORY ORIGIN.

1. *Due to strain,* as in some cases of fibrosis of the intima of the vessels.

2. *Neoplastic, e. g.,* fibrous tumors.

THE SYSTEMIC REACTION TO MICROBIC INJURY—INFECTION

The term infection is used in different senses by the pathologist and the hygienist. For our purposes, infection is a process; it consists not in the mere presence of pathogenic bacteria in the mouth, skin, or intestine, but in the growth of those bacteria in the tissues, in the diffusion of their products, and in the reaction brought about in the body by their presence. *Infection is the interaction between the body and the*

microörganism growing in it. This interaction may be local, and the process will, in that case, be one of infective inflammation already discussed; but we are now concerned with the general disturbances which follow such local growth, or the effects of a widespread proliferation of the microbes.

The hygienist, on the other hand, considers infection as the mere presence of the harmful microörganism; thus water, air, or a community may be infected; he distinguishes (1) **sporadic** infections, where isolated cases occur; (2) **endemic**,[1] where a notable number of cases of a given disease occurs year after year in a certain area, and (3) **epidemic**, where the disease suddenly affects a large number of people. Similarly, diseases of animals are sporadic, **enzoötic**,[2] and **epizoötic**.

Causation.—We have already considered the question of susceptibility to infection; it may be repeated that there are various ways in which susceptibility, inherited or acquired, may show itself, so that the opposition to the bacteria is less than normal; on the other hand, the bacteria may be of so great virulence that a normal power of opposition on the part of the body is not enough to protect it. Each case of infection is, therefore, the resultant of forces which are always varying; thus, there may be great susceptibility and virulent microbes, or great susceptibility and microbes of low virulence, or great power of resistance pitted against highly virulent microbes, or great power of resistance against lowly virulent microbes. The result differs in every case.

The Course of Infection.—To indicate the course of an infection a sketch may be given of a type case of typhoid fever. The patient on a given date has taken into his alimentary canal some typhoid bacilli. For a few days nothing is noted till symptoms of malaise appear— lassitude, slight but persistent headache, constipation, pain in the back, and so on. These grow worse instead of better, and ten days or so after the ingestion of the bacilli the patient is so weak and feverish that he takes to bed. This period has been the stage of **incubation**, during which **prodromal** or **premonitory** symptoms declare themselves, the stage continuing until the onset of a definite **febrile state**. For clinical purposes, it is customary to date the illness from the first prodromal symptoms, which generally correspond with a recognizable rise of temperature. The patient now has fever, general weakness, and various symptoms or signs referable to the different systems: (*a*) in the nervous system, there may be irritability or dulness, headache, and chilly sensations; (*b*) in the circulatory system, a rapid pulse, vasomotor disturbances, such as flushing; (*c*) in the digestive system, dryness of the mouth, by reason of diminution of salivary secretion, loss of appetite or a positive distaste for food, abdominal discomfort or pain, constipation, or at times diarrhœa with foul stools. Day by day the fever rises, and the symptoms grow worse; change of the urinary secretion is evidenced by diminution of the salts, notably the chlorides,

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[1] δῆμος, the people.   [2] ζῶον, animal.

and increase in other constituents, notably the urates; the characteristic eruption may show itself. In the early part of this stage the bacilli can be found in the circulating blood, and later the serum begins to gain the property of being able to agglutinate the typhoid bacilli. This is the stage of **fervescence**. Following this is the stage of high, **continued fever**, or **fastigium**, with persistence of all the symptoms and increasing weakness and loss of flesh. This may last for a couple of weeks, after which the fever begins to fall day by day—the stage of **defervescence**, which in turn is followed by **convalescence**, with a gradual return to health and strength. **Complications**, which are morbid conditions, either associated with the original cause or of other causation, may occur *during the* **course**, and **sequelæ** may *follow*. These latter are morbid states due directly or indirectly to the original infection, and are such happenings as abscesses due to B. typhosus or inflammation of the gall-bladder from the same cause; the latter may be a complication or a sequel.

The Period of Incubation.—The period of incubation is that time during which the growth of the bacteria is local and the disturbance local, and that time which follows during which the diffusion of the toxic products of the bacteria is not sufficiently great to give rise to general symptoms; as soon as these products have accumulated sufficiently they give rise to the prodromal symptoms. It is to be remembered that the prodromal symptoms may be due not only to the toxins of bacteria themselves, but to the toxic bodies (albumoses) made from body proteins by the enzyme action of the bacterial toxins. The period of incubation will be understood to vary according to the toxicity of the germ, the amount of toxin produced (that is, the number of germs present), and the resistance of the body.

Grades of Infection.—It might appear as if a line of demarcation were drawn between local infections and general infections, and yet the differences between the two are differences of degree, rather than of kind. The bacteria which by choice are of local occurrence may be found in the blood; lately, the diphtheria bacillus which was supposed to be strictly local in its habitation has been repeatedly found in the blood; the seat of election of the pneumococcus is the lung, but it also is found in the blood; the typhoid bacillus works its local effects in the bowel, but is found in the blood stream. It may be considered that every organism capable of local proliferation is theoretically capable of being found in the blood stream, and that in the case of organisms like the pyococci their presence or absence is due to the number of them that escape at a given moment, and the antagonistic power of the blood and the tissues. Further, with regard to the toxic products of bacteria, we are accustomed to designate their presence by the term **intoxication, sapremic intoxication**, or **sapremia**. This, again, is a matter of degree of intensity of the toxic products; thus, a mild local infection gives off a certain amount of toxin, and this is carried into the blood and tissue fluids, but is so diluted that we see no general bodily

change wrought thereby; we neglect such a mild intoxication, but it is nevertheless present.

Before leaving the subject of terminology, it is necessary to define the terms generally used; bacteria multiplying locally, and giving no visible signs of their presence in the blood, even if there be indication of **toxemia**, constitute a case of **localized infection**. If the bacteria not only multiply locally, but are also evidently in the blood, and are getting foothold in the tissues (metastases) the case becomes one of **bacteriemia**. Each of the metastases now becomes a centre for the production and diffusion of more toxin, so that with the bacteriemia the toxemia advances equally.[1]

For clinical purposes we are in the habit of making certain rough distinctions, dividing infections into: (1) fulminating; (2) acute; (3) persisting; (4) subinfection.

1. **Fulminating Infection.**—This type of infection is characterized by so great a flooding of the body by toxins, and presumably by the infective organisms, that the resistance of the tissues is notably ineffectual. The symptoms are those of great intoxication with depression of the functions; the heart beat becomes rapid and feeble, the blood pressure is lowered, the respiration is shallow and rapid, the patient becomes dull or comatose, and the temperature falls, becoming subnormal. If the disease is one ordinarily presenting a leukocytosis, a leukopenia is present. Such an overwhelming rapidity depends on a virulent organism, or a large number of such organisms, or a low resistance, or all these influences working together; but it has to be remembered that there are only certain bacteria which have the necessary virulence. It has never been possible, for example, to exalt the virulence of the tubercle bacillus to so great an extent as to produce this fulminance of symptoms. General bacteriemia,[2] scarlet fever, and epidemic cerebrospinal meningitis provide striking examples of it. So rapidly is the toxin produced, and so potent is it that it produces a degeneration of the walls of the capillaries, so that they burst, and petechiæ are produced; hence the purpuric rash that may be seen on the skin, and after death on the internal surfaces of such a case of intense infection; a marked hemolysis is also present.

It is a notable fact that these cases may exhibit, not only no rise

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[1] In our experience there is such painful confusion in the minds not only of students but of medical men in general between the terms septicemia, sapremia, pyemia, local and general sepsis or blood poisoning, that for the sake of clearness we prefer not to use them. There can surely be no doubt as to what is meant by toxemia and bacteriemia; they explain themselves. For the instruction of the student, we would say that, as popularly employed, localized septicemia is equivalent to localized infection, (generalized) septicemia to bacteriemia, sapremia to toxemia. Pyemia is by many used as a term to describe septicemia with metastatic abscesses, and "blood poisoning" as a euphemism for any or all of the above.

[2] A tendency is manifesting itself at the present time to speak of *bacteremia* instead of *bacteriemia*. Coming from the Greek βακτήριον, a staff, the latter is correct, but if it be earnestly desired to curtail the word, we suggest that there is the alternative *bactremia*, from βάκτρον, another form of the same word.

of temperature but even a subnormal one; this means that the cells of the body are not stimulated to that resistance which is evidenced by an increase of heat production, and metabolic processes instead of being rendered more active than normal are reduced to a low ebb.

2. **Acute Infection.**—This is the familiar form of infection which has been described, where in a non-fatal case there is a period of incubation, of fervescence, of continued fever, and of deferveseence. The gradual defervescence is called **lysis**; at times, as in acute pneumonia, the temperature falls suddenly, by **crisis**. The course of convalescence may be interrupted by **relapse** (a repetition of all or some of the symptoms of the primary infection); if this relapse occurs before the temperature has reached the normal level, we call it an **intercurrent relapse**.

3. **Persisting Infection.**—This is the form of infection generally called **chronic**, which is characterized by long continuance, during the whole of which time the infective agent appears to be at work. Examples of this type of disease are found in tuberculosis, syphilis, etc., as well as in occasional cases of infection by the ordinary pyogenic cocci. At times the smouldering infection bursts up into a blaze, and we note an **exacerbation**. Clinically, it is often the custom to divide these infections into **stages**, as is done in syphilis, but these have no special usefulness in the present connection, and it seems that, even among clinicians, this mode of classification of symptoms is falling into disuse.

Closely allied to the above infection, is the **remittent** infection, as it is seen in rheumatism; at present it seems as if more than one organism were able to cause this malady, but the characteristic to which we refer here, is that there is not with defervescence complete recovery or total destruction of the organism; the germ seems to lie latent, lighting up from time to time into an acute form of infection. The germs appear to work comparatively slowly and to develop neither a very high degree of intoxication nor so active a resistance on the part of the body as we are accustomed to see in the acute infections. We now recognize more and more fully the frequency of **latent infection**, of conditions, that is, in which for months and it may be years, pathogenic bacteria persist in the tissues or cavities of the body, setting up no disturbance, but capable at any moment of so doing. We may instance the now well-known "typhoid carriers."

Subinfection.—This term indicates a slight degree of infection such as is expressed by the presence of bacteria in the blood, which are not potent enough to cause gross symptoms of infection, yet which do actually wear out the cells whose duty it is to combat with and kill them. Normally, of course, bacteria are being carried away from the intestine and killed in the mesenteric nodes and in the liver; when, in addition to this constant action, we find that bacteria are locally active, and that there is a local inflammation in the bowel, if we examine the mesenteric node cells and the liver cells we find remnants of bacteria, often mere granules; the constant destruction of more than ordinary numbers of these means the more than ordinary wear and tear upon

the cells; liver cells, for instance, are thus the more quickly destroyed, and in many cases of cirrhosis of the liver, we believe this is a cause of the condition, though not the only one. It is not necessary that the organisms be very virulent; we think, in fact, that the ordinary bacteria of the intestinal tract can and often do constitute the agent in these instances of subinfection.

Terminal Infection.—It must have struck everyone who has had even a moderate amount of experience at the post mortem table that in cases of chronic disease, such as heart disease, where death has been gradual, there is frequently present some infection, such as a lobular pneumonia, or turbidity, from infection, of a long-present ascites, or what not. These infections we call **terminal**; and they arise not so much by virulence of the organism as by weakness of the body. We mean to designate by the words "terminal infection" those cases in which by reason of failing vitality a germ, powerless at ordinary times, is enabled to fasten upon the tissues and set up an acute inflammation. Such a process means that by reason of weakness of the body, a sub-infection becomes an acute infection, the terminal infection being set up by the chance microörganism which may be temporarily circulating in the blood.

THERMOGENESIS AND PYREXIA

Pyrexia is a heightened bodily temperature; the state of body in which a pyrexia exists, with all its concomitants, we shall call the **febrile state** or, briefly, fever.

Heat Production.—Heat is liberated from the organism under the following conditions:

1. From the food, *i. e.*, from the recombination of dissociated food-stuffs.

2. From katabolism, *i. e.*, from the oxygenation of tissue products. Metabolism breaks down the cell substance, and the products so obtained combine with oxygen, giving off heat in the process.

Fever is accompanied by increased heat production, and since the intake of food is generally diminished and the output of heat greater than normal, this increased heat production must be due mainly to tissue disintegration and oxidation. The student may well think of the febrile state as one in which the tissues are being "burned up."

Heat Discharge.—Heat is lost from the body by radiation and by evaporation from the surface, and by the passage of excreta. The discharge may be increased, and the body temperature lowered by dilatation of the surface vessels, by increased amount of sweat, and by increased respiration, in which more air than usual is passed over the respiratory surface and warmed, and the evaporation in the lungs thus increased. This increased respiration (panting) is the means by which the dog, unable to perspire, cools itself.

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We express heat frequently in terms of **calories**, a calory being the amount of heat necessary to raise 1 gram of water 1° C. at normal atmospheric pressure; of the total diffusion from the human body, less than 2 per cent. is lost in the urine and feces, less than 4 per cent. in the expired air, 7 per cent. by evaporation from the lungs, 15 per cent. in evaporation from the skin, while 73 per cent. is lost by radiation and conduction from the body surface.

The lower the temperature of the medium in contact with the body, the greater the loss of heat; if the external temperature be higher than that of the body, and the air be so saturated with moisture that evaporation is prevented, the body actually gains heat.

In spite of the variation of heat production and of heat discharge at different times, the temperature of the warm-blooded animal is very constant (save in hibernating animals during hibernation), whereas cold-blooded animals have a temperature varying with the external medium (**poikilothermic**). The adult healthy man has a temperature (rectal) that varies little from 98.9° F. A bodily temperature of 107.5° is generally considered the upper limit of temperature that is compatible with continued life, although, of course, instances to the contrary are here and there met. The lower limit is considered 93° F., with similar qualifications.

Heat Regulation.—With conditions of heat production so complex, a constant temperature maintained speaks for a heat-regulating mechanism, even if we did not know that there are two sets of sensory nerves, one for heat and one for cold; also, injury or stimulation of certain areas of the brain or medulla raises or lowers the bodily temperature. In short, there is good reason to suppose that there are in the brain, or the cord, or in both, cells, some of which on stimulation cause an increased production of heat, others an increased loss of heat; these cells are affected in various ways, for example, reflexly, or by the temperature of the circulating blood, or by substances in the circulating blood that act upon them. So perfect is the result that it seems hard to think of the mechanism otherwise than as controlled by one centre or a pair of closely connected centres. It must always be remembered that the thermometer gives us information only as to the balance or resultant between heat income and heat expenditure at a given moment in a particular part of the body; we gain, therefore, by the use of this instrument, no accurate measurement of the *amount* of heat developed or lost.

FEVER, THE FEBRILE STATE

Fever, or the **febrile state**, is the train of symptoms and changes in the organism which constitutes the reaction to infection, which changes, although associated with increased heat production, may occur with or without rise of temperature (be **febrile** or **afebrile**), and the rise of temperature itself is best known as **pyrexia**. The febrile state is associated with changes in the circulatory, nervous, muscular, respiratory, digestive and excretory systems, which we shall take up in order.

Pyrexia.—In an infection we can frequently recognize the **fervescent** or **pyrogenetic**, the **continued febrile**, and the **defervescent** stages; the last named may be very short, the temperature descending sharply, by **crisis**, or gradually, by **lysis**.

We are wont to distinguish the varieties of fever as **continued**, in which the changes between maximum and minimum are as slight as in health, but at a higher level; as **remittent**, where the changes in a day may range over several degrees, as happens in bacteriemia, suppuration, and tuberculosis with secondary infection; and as **intermittent**, where a succession of febrile attacks, each with its fervescent, continued, and defervescent periods, occur separated by a continuous interval of normal temperature of a day's or more duration—as in malaria. Where several days elapse the fever is called **recurrent**, as in relapsing fever.

The Associated Disturbances.—Disturbance in the Nervous System.— *Chills and Chilly Sensations.*—It happens often in the fervescent stage of infections that the patient feels cold, the teeth chatter, and yet, in truth, the surface may be hotter than normal, and the temperature high, and increasing in height. The face and extremities may be pale. This pallor or local anemia suggests that the blood is attracted to other organs, making a corresponding congestion somewhere, and that there is a storage of heat in the body for the time. The chill is evidently a phenomenon incited from the central nervous system; in fact, the chill may occur without exposure to cold or infection, in which case it appears to be wholly a part of the function of the nervous system. Closely associated with the phenomenon is the **rigor**, in which fine fibrillary contractions of the muscles of the surface occur, involuntary in nature. Clinically, the term rigor is used to denote the entire occurrence, including the chill. No visible muscular action results from the rigor; in fact, opposing muscles synchronously contract, with the total result of a stiffening of the muscle as a whole (which is the strict significance of the word rigor). When the muscle fibrils are active, just like the flapping arms of the chilled coachman, these rapid contractions mean work, and muscular work means the giving off, into the body, of heat.

Other Febrile Nervous Disturbances.—Here we refer to the effects produced upon the whole mechanism, indicated by the state of the central nervous system. These are periods of nervous irritation and nervous depression. In some cases of fever, there are headache, irritability, photophobia, sleeplessness, hallucinations, and active delirium; in others, apathy, mental dulness, prostration, inability to control or notice the passage of excreta, quiet delirium, and coma. We may consider that these phenomena are the result of the toxins acting upon the cells of the brain and cord, especially as we know that certain toxins have a direct affinity for the nerve cell body and its parts.

Disturbance in the Circulatory System.—The febrile state, in general, is accompanied by a marked increase in the rate of heart beat, evidenced by increased pulse rate. With this there may be a softer pulse, with

dicrotism, indicating arterial dilatation and lowered blood-pressure, or a full bounding pulse, so that it is even still a custom to divide fevers into the **sthenic**—those characterized by a morbid excess of vital, especially circulatory energy—and the contrary **asthenic**. These determinations are usually made only by observation of the pulse, which is affected in any given case by so large a number of factors that our deductions are not of much value. One thing we do know, however, is that many toxins of infective disease directly influence the cardiac muscle cells to degeneration, and not only these, but the nerves which control them, so that a toxin such as that of diphtheria is able to cause sudden death.

Disturbance in the Blood.—Infection even of a mild grade is able to cause a lysis of red corpuscles; the effect upon white corpuscles is variable. Most kinds of infection are attended by a distinct increase in the leukocytes in the peripheral blood (**leukocytosis**), but some, like typhoid fever, are attended by a lowering of the number (**leukopenia**). In such a disease, a rapid rise in the leukocyte count indicates that a secondary infection has supervened; but it must also be remembered that a secondary infection may supervene without a leukocytosis, because the reaction of the body may be insufficient; in such a case, the very absence of a leukocytosis in the presence of a secondary infection is of bad prognostic import. Similarly, in an infection in which we are accustomed to find a leukocytosis, its absence is not of good import because it suggests lack of reaction on the part of the patient. The increase in the white cells is usually in the polynuclears in acute cases, in the lymphocytes in the slower, less intense infections, such as tuberculosis, and in the eosinophiles in certain states where animal parasites are present, and in certain infections of the skin and also in whooping cough.

Disturbance in Respiration.—The respiratory movement is quickened in infections. This quickening is brought about by anything which increases the temperature of the blood bathing the respiratory centre. The rapid breathing has the effect of increasing the evaporation in the lungs, and diffusing more heat than usual because more air is being warmed. The increased temperature of an infected patient and the infection itself favor increase of metabolism, and the increase of metabolism leads to increased tension of carbon dioxide in the blood, which, in turn, is again one of the important causes of the increased rate of respiration.

Disturbances in the Urinary System.—The effect of fever is to diminish the water of the urine, and the chlorides and phosphates, and to increase the degree of coloration, the urea, the uric acid, the kreatinin, and the potassium salts. The diminution in water is due partly to lowered blood pressure and partly to the increased secretion by the skin and evaporation from the lungs; the diminution in chlorides is not satisfactorily explained. The increase in potassium salts is due to the large number of red cells that have been broken up; the urea and

uric acid and other nitrogenous derivatives are the result of a metabolism that is more active than usual and of the breaking down of proteins, which proteins are not all food and reserve materials, but are in a large part those of the tissues.

In most severe infections the urine contains albumin, and the kidneys are the seat of a cloudy swelling or worse; this parenchymatous change in the kidney is probably due to change wrought on the epithelium by the toxins themselves and also by the poisonous products of tissue disintegration. This state of the urine is generally described as "**febrile albuminuria**," and the urine secreted during an attack of infection is itself toxic to animals; the toxins more or less altered appear in the urine, and they damage the kidney on their way through.

Disturbance of the Digestive System.—It is well known that loss of appetite and distaste for food are frequent results of infection, but the physiology of the process is not yet clear; the glandular secretions are lessened in amount, as is seen in the dryness of the mouth and throat. Accessory digestive glands, in fact all the glands of the body, are influenced by the toxins, and cloudy swelling results with, no doubt, a corresponding lack of efficiency of the gland for the time being.

The Causes of Pyrexia.—The most prominent cause of febrile temperature is infection, but there are sundry other causes of pyrexia which require mention. The infective microbes act through their toxins, for pyrexia can be produced experimentally by toxins, as well as by enzymes and ferment-like bodies. The hemolysis following upon an internal hemorrhage, or upon the injection of blood into the system or upon the injection of a large quantity of water, is accompanied by pyrexia. The sterile extracts of tissues or tissue juices are similarly capable, as occurs with the formation of infarct, though uninfected, or after burns and scalds; even the injection of the extract of thyroid may be followed by a febrile temperature. According to Vaughan, all foreign proteins gaining entrance into the system induce pyrexia as the result of their absorption and dissociation by the cells, and the bacterial proteins are no exception. Drugs, such as hydrogen sulphide and sometimes strychnine, have the power of raising the temperature, and continued exposure to a high surrounding temperature will also prove effective. Irritation of the heat-producing mechanism by way of the nervous system induces pyrexia of another order. We have already referred to the experimental evidence of the existence of this form. Clinically it is to be observed after certain injuries to the central nervous system, and possibly it explains the pyrexia of sunstroke. We are not yet able to supply the explanations necessary for the grouping together of all these varying cases, but the infective, the enzyme, and the tissue-extract reactions are somewhat similar, and all of these are cases where reaction leads to the production of antibodies; just as inflammation is the reaction to local injury, *fever is the process of adaptation to such toxic agencies as can be neutralized by the development of antibodies.* If the toxin be so strong as to kill quickly, and without strong systemic reaction, we find that *death is*

preceded by arrest of the febrile reaction and by a falling temperature; the apparent exceptions, in which death occurs in hyperpyrexia, may be cases in which a specific action on the heat centre is produced.

It is perhaps unwise to attempt to find a purpose for every morbid phenomenon when our ignorance is still so abysmal; nevertheless, in the febrile state, knowing how increased heat stimulates the cells to more active metabolism, it is difficult not to suggest the opinion that both the nervous disturbances leading to heightened bodily temperature and the direct action of the toxins upon individual tissues, in fact, all the phenomena of fever, lead up to and favor that increased activity of the body cells which results in the production of specific antibodies, and that at an accelerated rate, so that thereby the specific toxins are neutralized and recovery is aided.

IMMUNITY

In the course of infections and diseases set up by certain organic substances, the body develops certain antibodies by which the toxins are neutralized, so that the disturbance comes to an end. This is the process of immunization. It has already been indicated that the body has a certain immunity, absolute or relative, to deleterious outside influences of many kinds, which immunity is only another name for the accustomance to surroundings; the body, further, has immunity which is inherited. We know of certain acquisitions of immunity which are gradual; and when we study the question of immunity experimentally, it is only those cases in which the immunity is produced in the course of a short time that lend themselves to our experimental study. We thus know little about immunity, save as it is produced in connection with some toxins, enzymes, and tissue juices.

Non-specific Immunity.—In our discussion of the defences of the body we pointed out that if microbes of various orders be introduced in small numbers into the tissues, unless they be of extraordinary virulence, they are destroyed in a very short time. In other words, the cells of the body have a defensive power which may be used indifferently against various intruders. And even where we deal with the development of an acute specific disease, we notice this striking fact, that the microbes of that disease are not to be found growing throughout the whole body. Take, for example, a case of malignant endocarditis; the very fact that the heart valves are singled out, is in itself an indication that the microbes, streptococci, or what not, have been circulating in the blood, and the very nature of this disease necessitates that the microbes are from time to time being swept off the valves into the blood-stream and carried now to this, now to that organ elsewhere in the body. But the remarkable fact is that in such cases we never find abscesses forming in the muscles, and very rarely in the brain, or save in cases of phlegmonous gastritis—and they are distinctly uncommon—in the submucosa of the alimentary canal; and yet all

these tissues have an abundant blood supply. Numerous similar instances will be called to mind, and the only conclusion that we can draw is that while certain tissues or organs are peculiarly susceptible to the inroad of one or other species of bacteria, coincidently other tissues are characteristically insusceptible, or, in other words, are engaged in destroying these organisms and preventing their growth, or, in yet other words, possess a local immunity. The muscular tissue or, more accurately, the endothelium of the vessels supplying the muscles may be cited as a well-marked example of this non-specific immunity, because no matter what bacteria attack the body they do not make a foothold here, bacterial infections (as distinct from the subinfections noted on p. 200) of the muscle being very rare. We mention these facts because it seems that this capacity on the part of these tissues of destroying bacteria, without any previous apparent education, must be the foundation upon which is built or developed the specific immunity toward particular species of bacteria, which we shall immediately discuss. Or, otherwise, the development of specific immunity is not to be regarded as a new property or acquirement, but as an exaltation of properties already possessed by the tissues, and if this be so it must be kept in mind that in each disease that attacks the body this non-specific immunity is constantly at work, hand in hand with specific immunity that is gradually being developed. These views are supported by the more recent observations of Abderhalden on the increase in common as distinct from specific proteolytic enzymes in the blood in the course of a few hours after the injection into the body of various proteins.

Immunity against Substances of Known Constitution.—It is known that the so-called "arsenic eaters" of Styria can, after a few years' addiction, consume without ill effects four times the ordinary fatal dose of the drug, and while this has not been confirmed with animals, nevertheless, there is evidence of a certain grade of immunity that can be conferred on them. If an arsenical salt be injected into the peritoneum in suspension or solution, a fatal dose is accompanied by a diminution of the leukocytes that are found so abundantly in the peritoneal fluid—a negative chemiotaxis is excited. If the dose be not fatal, there is at first a reduction, followed by a great increase in the number of the leukocytes, so that the peritoneal fluid may appear milky, and the leukocytosis in the circulating blood becomes very evident. Whether a suspension or a solution of arsenic be employed, the leukocytes are found to take it up, and the larger the dose, provided it be not fatal, the more pronounced is the leukocytic increase. In time, fixed phagocytes also take up portions of the arsenic, which, in fact, specially tends to find its way to the liver. The fatal effects are evidently wrought upon the nervous tissue, which is susceptible to such an extent that one one-hundredth of the subcutaneous dose is fatal if injected into the brain. In producing immunity, a rabbit is taken of such body weight that 10 c.c. of a given solution produces death in forty-eight hours; 2 c.c. of this solution is injected at night, followed

by 10 c.c. (the fatal dose) next morning; but no ill results ensue. Arsenic is slowly eliminated; the animal has 12 c.c.—more than a fatal dose in its body; death does not occur because the first dose has excited an excess of leukocytes, which are, so to speak, lying in wait for the second dose to be injected. This is, if not true immunity, at least a form of positive protection, comparable to the protection to be spoken of later in discussing "Issaeff's resistance period" and to the non-specific immunity that has just been discussed. But there is more to be said. If after six or eight days this animal be bled, the serum of the blood is found to have acquired a new property; 8 c.c. of it, injected into a fresh rabbit along with, or slightly before a minimal fatal dose of arsenic, prevents the death of the animal. This prevention is the conferring on the fresh animal of **passive immunity**; a substance not made by the animal itself, but introduced into its body, acts as an antidote—aids the body tissues in neutralizing or destroying the poison. The serum of the actively immunized animal contains something that it did not contain before the immunization. What is this something? We do not know; but we do know that it is not arsenic containing, is not a combination of the arsenic and the cell substance of the animal. The cell substance has elaborated something which is capable of combining with or neutralizing arsenic, something which is capable of solution in the serum, and of remaining in it for eight days at least. We are not unaware of the criticism to which the interpretation is open, but for clearness we refrain from stating the full argument for and against. That animal organisms can protect themselves is indicated by the existence of "arsenic fast" trypanosomes. If a dose of atoxyl or other arsenic compound insufficient to kill all the trypanosomes be given to an animal suffering from trypanosomiasis, it is found that later doses frequently have little or no effect. The parasites which have survived are unaffected by arsenic, though they may succumb easily to mercury or antimony salts.

Immunization against Albuminoid Vegetable Poisons.—Phytotoxins. —There are certain vegetable poisons of a proteid nature, distinct from the alkaloids and glucosides, extremely toxic, to wit, **abrin, ricin, robin,** and others. Of ricin, one grain is sufficient to kill a million and a half guinea-pigs, and this not suddenly, but after a period of four or five days, subsequent to which œdema, inflammation, and necrosis of the tissues near the point of injection set in; this suggests the existence of a ferment-like action with formation of some second substance able to act upon the cell substance. If animals be fed cautiously upon slowly increasing doses of ricin, they gain such immunity that they can take a hundred times the fatal dose with impunity, and by injection the immunity can be made so active that they can take five thousand times the fatal dose. If the serum of such an animal be mixed with the poison, the injection of the mixture into an animal produces no ill effects, the poison being rendered inert.

Ricin has two properties—its toxicity, and the power in toxic doses to cause agglutination of the blood corpuscles; outside the body it can

cause agglutination of the corpuscles; but by the action of pepsin and hydrochloric acid this agglutination power is destroyed *without the toxicity being diminished*. Either ricin is a mixture of two substances, or, what is more likely, it consists of a very complex molecule which can undergo slight chemical change without its specific functions being destroyed. We may assume the latter, and show what some of these changes are; if heated to 100° C. for two hours, it loses all its toxic powers, yet animals treated by it become immunized. The so modified toxin (called a **toxoid**) is no longer toxic, but is capable of setting up the changes in the body necessary to the formation of an antibody. If, again, ricin be added to the serum of an immunized animal with its **antiricin**, so that the mixture is inert and unable to produce toxic effects, and if the mixture be injected into an animal of the same species as yielded the antiricin, it still has the power of producing active immunity; from this it is evident that in the mixture of toxin and antitoxin the toxin is not destroyed.

Once an animal is immunized against ricin it may be bled again and again and the blood remains antitoxic; the tissues have evidently acquired the power of producing and discharging the antitoxin, so that it does not seem likely that the antiricin is derived from the ricin. The vast preponderance in quantity of the antitoxin over the toxin also tells against such a supposition. *Evidently the antitoxin is a substance wholly new to the organism*, produced primarily by the cells as a reaction to the presence, in them, of the toxin.

Immunization against Substances of Unknown Constitution.— Enzymes and Anti-enzymes.—If a foreign enzyme be injected repeatedly into the body, a tolerance of it is acquired, by means of an anti-enzyme which is formed. For example, goats injected with rennet produce a serum which has the power of neutralizing rennet, and this in a quantitative degree, so that a fixed amount of serum neutralizes a definite amount of rennet of a known strength. But just as an animal immunized against a certain microörganism is not rendered immune to other, although closely related, microörganisms, so in the above case the blood serum will not neutralize the effect of "rennets" obtained from plants. Thus the anti-enzyme is strictly specific. The process of immunization against animal and vegetable enzymes seems at first sight very like the process that exists in immunization against bacteria; but there is this important difference, that the development of anti-enzyme is limited. The supposed reason for this is that the anti-enzyme set free in the body stimulates the cells to set free an anti-anti-enzyme.

Anti-enzymes exist in the body in the normal state; an antirennin is present in normal blood, and antipepsin exists in the stomach mucosa, and an antiferment to the digestive action of the pancreas can be isolated from that organ. If it were not for these antiferments the juice of the stomach would digest the coat of the stomach as it digests meat, and the pancreas would digest itself in life as it does after death.

Despite the existence of antipeptic and antidiastatic enzymes, they cannot be artificially produced by the use of pepsin and diastase, nor does the injection of fibrin ferment result in the production of an anti-fibrin-ferment. The reason for this probably is that the enzymes that are produced all through the body (for pepsin, diastase, and fibrin ferment can be produced by the cells of all organs) are so usual to the cells that they do not excite any antagonistic action.

Toxins and Antitoxins.—One of the early discoveries in bacteriology was that of the bacteria-produced toxins; this was made out especially for diphtheria and tetanus bacilli, which we now know are able to produce and give off diffusible toxins, the **ectotoxins**. Most bacteria produce **endotoxins**, which are not diffusible. The injection into animals of the diffusible toxins was found to produce immunity; the serum of an animal, so immunized, contains substances which neutralize the diffusible toxins, either outside or in the body, and these are the **antitoxins** of medicine and commerce. It became necessary to arrange a standard by which to measure these antitoxins, and this was done by determining how much would neutralize the unit of toxin, which is *the smallest amount that suffices to kill a 250-gram guinea-pig within four days*. The production of antitoxin is a vital process, while the neutralization of the toxin appears to be purely a chemical one of the nature of a loose molecular union; toxin by itself can pass through gelatin filters, but when acted upon by antitoxin fails to do so, that is, the resultant of the interaction is a larger (compound) molecule.

It is not possible to define the term **toxin** accurately; toxins are substances that act in minute doses, that diffuse with difficulty, that are products of cell metabolism, and that have not yet been separated in a pure state (see also p. 83). We can define them as poisons against which it is possible to obtain immunity by the production of antibodies, and we can state that they appear to be colloids, and that they are allied to proteins, but do not give the full series of reactions characteristic of the typical protein bodies. They may, however, be dissociation products of proteins. Whatever toxins be, it is nevertheless possible to speak quite definitely of **toxin action** as a process similar to enzyme action; toxin action is a physical property, dependent upon molecular arrangement and shared by some, at least, of the dissociation products of the cell. From the very vagueness of the term toxin it has within the last few years become the custom to speak of **antigen**, thereby denoting any substance which, introduced into the tissues, leads to the production by them of **antibodies** (antitoxin, anti-enzyme and the like.)

Toxin action is the first essential in the production of antitoxin. If a non-lethal dose of toxin be injected into an animal, it disappears in a few minutes, because it is taken up by the cells of different organs and by the leukocytes, and can in most cases be recovered from the organs. And here is the crux of the experiment. If tetanus toxin, well known to act upon the nervous system, be injected, it disappears, and can be recovered from all the organs, *except the nervous system*.

Does this mean that the nervous system has none of it? Quite the contrary; all the other systems give it up readily because their cells have not entered into a hard and fast combination with it, whereas those of the nervous system have. This close binding or anchoring of the toxin in a tissue is the condition necessary to the production of the anti-toxin, and it seems to be the case that *the tissues that bind the toxins closely are those that develop the antitoxins.*

FIG. 38

It is not necessary for the production of antitoxins that the toxins produce disease; the toxin may by heat be rendered harmless (toxoid), and yet when injected can cause the production of antitoxin. This means that there are in a toxin molecule at least two parts, one of which is concerned with producing the toxic effect. If this toxic part be rendered inert by heat, of what does the remainder of the molecule consist, and what does it do? Since such a modified toxin can set up immunity it is clear that it must have attained close union with the cell protoplasm; therefore, Ehrlich concludes that there is a part of the cell devoted to the function of fixing the toxin molecule to the tissue molecule, and this part of it is called the **haptophore**; the part of the molecule which is actually toxic to the cell body when fixed to it is called the **toxophore**. This is represented graphically in Fig. 38.

It is evident from proof that we need not here give, that the cells which thus become combined with the toxin molecules are those that produce the antitoxin, and that the toxin is not in any sense changed into antitoxin. It is evident that the haptophore of the toxin molecule does not do all the "binding" by itself, otherwise it could fasten upon any cell of the body, and this power it obviously does not possess. There must be a degree of receptivity on the part of the cell. A shunting engine may have a coupler, but it cannot couple to a car unless the car also has a coupler. Ehrlich has devised a conception in graphic terms of the process. If we say that a toxin molecule has a certain coupler, it follows that the cell must have one to fit it; but the complex cell has to provide couplers adapted not only to the coupler of the toxin molecule but to various other molecules—other toxins, food-stuffs of different sorts, and so on.

These adapted couplers of the cell molecule, adapted to many different forms of couplers on foreign molecules he has called **receptors**, or
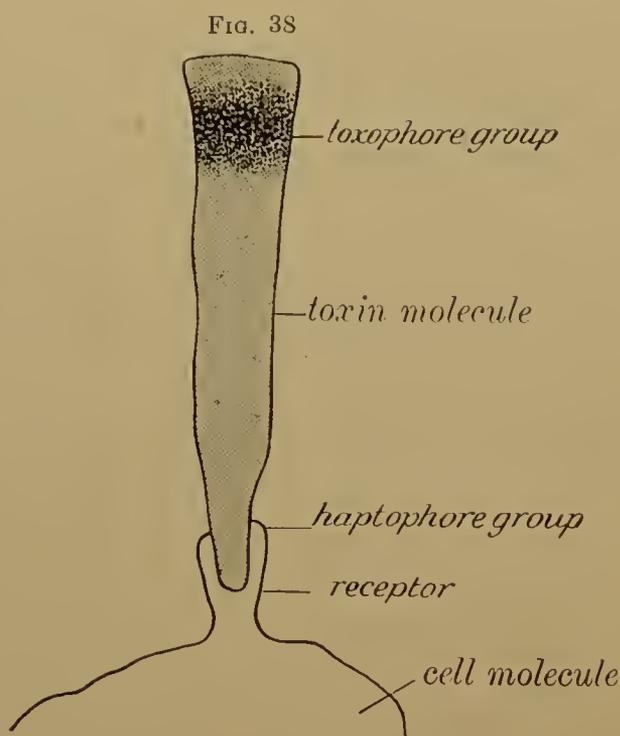
side-chains. From one's chemical study, it will be recalled that we depict these side-chains as reaching out for certain substances to satisfy them—they are **unsatisfied affinities**. To go back to the picture of the toxin molecule, it will be seen that the side-chain is reaching out to satisfy its affinity for the *haptophore* part of the toxin molecule, that coupler attracts coupler. It does not matter whether there be a toxophore part of the molecule or not; the toxophore part of the molecule has no power of satisfying the side-chain, and cannot couple with it; but if the haptophore part join with the cell the toxophore part is brought into direct connection with the cell, and the toxin can thus become part of the cell; in other words, can attack it. To apply this to a practical case, let us take that of diphtheria antitoxin; the toxin molecule fastens on a cell by its haptophore part and its toxophore part acts upon the cell; as a consequence the cell throws out many additional side-chains, antitoxin molecules, which become free in the blood; the toxin molecules pick these up, couple with them, and so are satisfied without reaching the cell at all.

Fig. 39
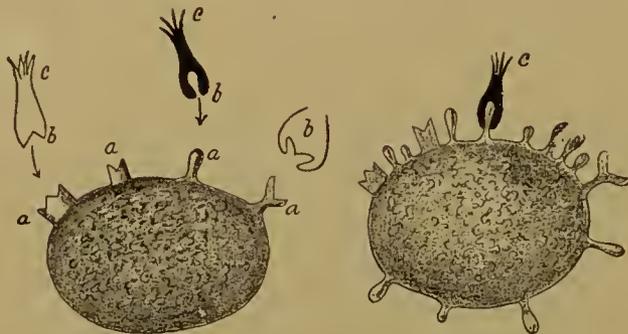
Ehrlich's conception of the cell molecule. Molecules with various receptors or haptophorous groups of the first order (*a*) adapted to combination with the haptophorous groups (*b*) of various chemical compounds brought to them. It will be noted that there is no mechanism by which the toxophorous elements (*c*) of the compounds can be directly attached to the cell. (McFarland, after Ehrlich.)

There is a normal discharge into the blood plasma of a large number of potential antitoxins, quite apart from the stimulus of special toxins, so that one is tempted to think antitoxins may not be so purely specific as has been stated. Ehrlich's "side-chain" theory supposes that a cell once stimulated to perform a certain act does not necessarily cease doing so when the immediate need is past, but keeps on producing them continually even after the stimulus has been removed. The toxin molecule stimulates the cell to throw out receptors like the receptor which first fixes it. It is supposed, in terms of the theory, that these fresh receptors are continually thrown off and constitute the antitoxin. It is convenient, but difficult, to understand how this thing happens, and at this point we propose to indicate a modification of the side-chain theory as it is ordinarily understood. As we have indicated before, the cell consists of cytoplasm and nucleoplasm, not to lay stress upon the paraplasm. When a toxin becomes absorbed into the cell, we do not

picture it so much as fixed to the biophoric molecule, as lying loose in the cytoplasm and combining with the side-chains of the biophoric molecule, dissociating them from the molecule. If there are enough of such toxin molecules, the biophoric molecule loses side-chains so rapidly as actually to be destroyed, "pulled to pieces." This does not mean that there must be a toxin molecule for every side-chain detached, but rather that enzyme action, as we have explained it, must play a part, and that a toxin molecule, having detached a side-chain is free to break itself away from it, and at once fix upon and detach a new side-chain and another and yet another. Only upon some such assumption, we think, is it possible to explain satisfactorily the cases where a minute amount of toxin can kill large animals. We think that poisons, other than toxins, wreak their effects by a single act of union with the biophoric mass, while the toxins must be able to act like ferments, with a repeating action. If we were to suppose that the toxin molecule made a single act of union with a side-chain, it is hard to see why the dissociation of a single side-chain should at once cause the biophoric mass to set free a large number of similar side-chains; but if the toxin molecule should be able to repeat this act in quick succession again and again and yet again, we can imagine the cell establishing a habit in the production of the new side-chains. It will be understood that this implies activity of a high order in the biophoric molecule: it is precisely this activity that marks the resisting cell as different from the cell against which the toxic attack is at once successful in causing cell death. Let us digress here to give an example: instead of the abstract toxin molecule, read tetanotoxin, instead of the biophoric molecule consider a single cell of nerve tissue; the tetanotoxin joins with the receptor for it and detaches it, and freeing itself from the receptor it has taken up, there begins a race between toxin and cell, as to whether the cell can produce more receptors than the toxin can detach; if it can, the excess of them, continuing to be thrown off, constitutes tetano-antitoxin, and thus a relative immunity is the result of an unsuccessful toxin attack, just as the soldiers of a garrison become more efficient by reason of each occasion on which the invader attempts but fails to capture their stronghold. It will be seen from the above that our conception of immunity depends upon the toxin hovering, so to say, in the cytoplasm, and not upon it being part of the biophoric molecule. Our idea of antitoxin production is expressed graphically in Fig. 40, the thorough study of which we would counsel.

The Mode of Union of Toxin and Antitoxin.—If toxin and antitoxin be allowed to unite, neither is necessarily altered in the process, because at least one of them can be separated unchanged from the mixture; further, toxin neutralized by antitoxin may be neutral for animals of one species and poisonous for those of another, which may be explained by the statement that there are, in the blood of the second animal, substances with so strong an affinity for the antitoxin that they unite with it, detaching it from the toxin, which is thus left free to act. If

FIG. 40
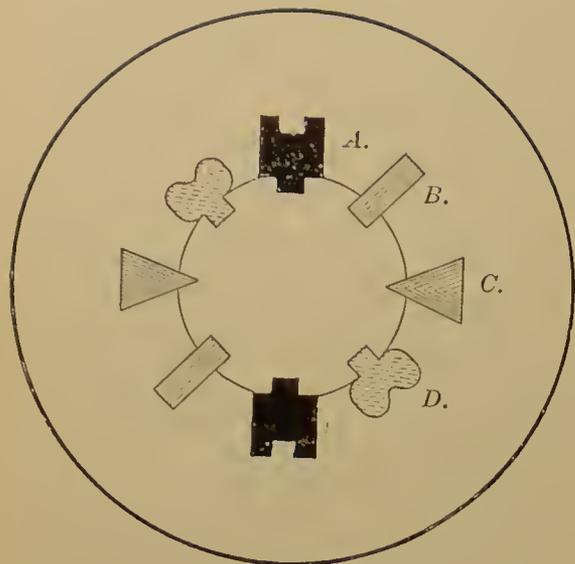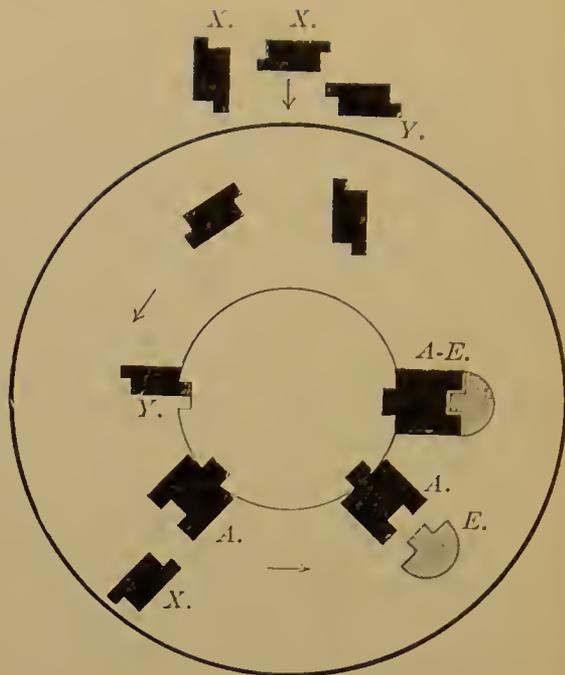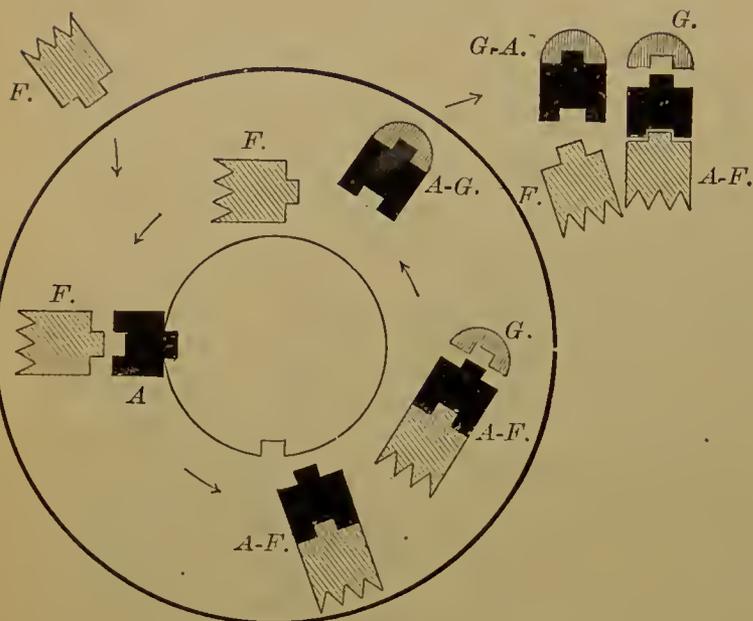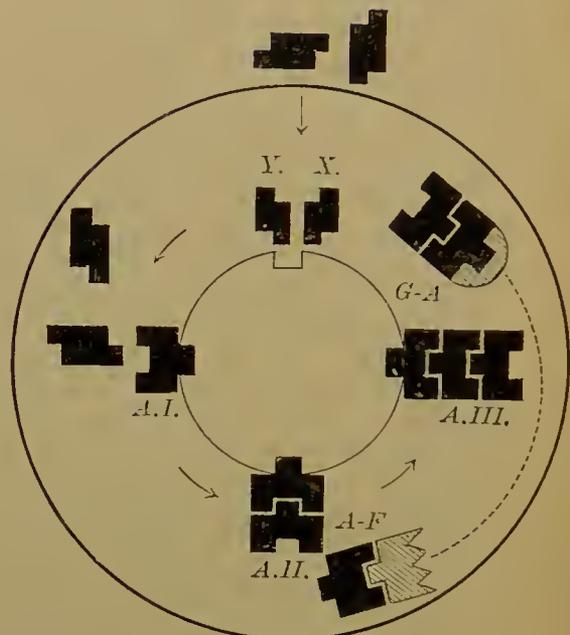
The authors' conception of side-chain and antitoxin production: 1. A biophoric molecule situated within the cell, and possessing side-chains of various orders, A, B, C, D. 2. Mode of formation of side-chains; free molecules (X, Y) diffuse into the cell (or are produced within the cell by dissociation of more complex molecules, also absorbed); these are attracted by an unsatisfied affinity of the biophore, and are built up by it to form the side-chain A; such side-chain, when formed, may become satisfied by attracting to it other (foodstuff) molecules such as E, having the right order of haptophorous grouping; it is conceivable (but not shown in the diagram) that molecules of the E order may not merely satisfy the side-chain, but detach it so that the compound A–E becomes free in the cytoplasm, or discharged from the cell (active katabolism). 3. A toxin molecule F, diffusing into the cytoplasm has a stronger affinity for the side-chain A than has the biophore, combines with it and detaches it; but when detached and free in the cytoplasm other molecules (G) present in the cytoplasm have now a stronger affinity for the A moiety of the compound A–F and combine with it, liberating the toxin moiety F, which again becomes free in the cytoplasm and capable of dissociating another side-chain A; or the compound G–A may become discharged from the cell (circulating antitoxin), and then in the altered surroundings the extracellular toxin molecules F may exert the greater affinity and joining with the A moiety become neutralized; it is the G–A compound, and not the side-chain A alone, that constitutes the extracellular antitoxin. 4. In the presence of abundant X and Y molecules the side-chains A become built up in series, and this whether attached to the biophore or free in the cytoplasm; the more there are freed by the action of the toxin, the greater under these conditions will be the production of antitoxins; thus the presence of the toxin molecule F stimulates the cell to the production of increased numbers of the molecules of the particular side-chain order upon which it exerts specific action.

toxin and antitoxin be allowed *in vitro* to act one upon the other, they become more closely bound one to the other, and *in vivo* the longer the toxin acts in the cell the more firmly does it become fixed to the receptors, and the more difficult is it for the antitoxin to detach it; thus the later in the course of the disease the antitoxin is injected, the less chance it has of being effective. The very fact that antitoxins can enter the cell and arrest the infective process bears out the supposition that the toxins when they are setting up cell disturbances are not actually fused into the biophoric molecule, but are acting upon it from without, that is, in the cytoplasm. The action of antitoxin seems to be that: (1) it neutralizes free toxins in circulation, so preventing their action upon the cells, and (2) it gains entrance to the cells and there detaches toxin molecules, thereby setting up the excess of receptors necessary, as well as neutralizing the toxin molecules temporarily set free.

Just as enzymes cause the development of anti-enzymes, so other diffusible-cell products, particularly proteins, have a similar power.

Precipitins.—If the culture fluid, in which certain germs have been grown and from which they have been removed, be injected into the animal body, there appears a substance—an antibody—in the blood serum, so that it, added to the original culture fluid, causes a precipitate of the proteins in that fluid. These antibodies were originally called **coagulins** and, later, **precipitins**. This power is possessed not only by germ-free culture fluids, but by many proteid substances of animal and vegetable origin, such as milk, egg albumin, horse serum, globulins from blood, albuminous urine, pleural exudate, vegetable proteins such as edestin, hordein, etc. The action of these is remarkably specific; for example, if human blood serum be injected into rabbits, the rabbits' serum causes a precipitate in human serum, but not in dogs' or goats' serum, and this constitutes a valuable medico-legal mode of deciding if a blood stain be caused by human or by other blood. But, still dealing with this example, although the treated rabbits' serum might not cause a precipitation in dogs' or goats' blood, it may in that of the gorilla or the orang, because of the relationship that exists between man and these animals. The more nearly two animals are related, the greater likelihood is there that the proteid substances in their blood are the same, or similar, and that they will give rise to the same or similar antibodies or precipitins. Nevertheless, the precipitation is most marked with the homologous serum, that is, the serum of the species originally used in the experiments, and one may go farther and note that the most marked precipitation of all will occur with the serum of the *individual* that supplied the original serum.

The different proteins in a blood serum have something in common, so that the precipitin developed by the injection of one protein may act upon other proteins in the blood; thus if *serum*, free from blood cells, be injected, the antibody so produced, when added to *whole blood*, can produce hemolysis (see p. 161).

In these experiments, the **precipitable** substance is considered to be

the main proteid substance of the fluid that is used, and we suppose
that the action is definitely specific for each protein, even though this
implies that there is an enormous number of proteins, each different
from another. As there are toxins and toxoids, so there are precipitins
and precipitoids and even antiprecipitins.

Agglutinins.—Agglutination consists in the clumping of free bacilli
in a fluid medium when there is added to that medium the serum of
an individual previously inoculated with bacteria of the same species.
With this clumping, the bacteria, if previously motile, become motion-
less. This constitutes the Widal reaction which is in common use, with
this difference that in the latter the converse procedure is carried out, so
that the result shows whether the individual affording the serum has
or has not been infected with typhoid bacilli. Agglutination tests
can be done with non-motile as well as with motile organisms, and are
obtained with the organisms of typhoid, dysentery, tuberculosis, plague,
anthrax, cholera, and with Bacillus coli, pyocyaneus, pneumococcus,
streptococcus, and staphylococcus. Agglutination is specific to this
extent, that with *relatively high dilutions* of the homologous serum, the
particular organism concerned is the only one to show clumping. The
reaction can be observed under the microscope or in bulk, where in
small tubes the formation of a flocculent sediment is seen; living and
dead bacilli alike produce the phenomenon, and the injection of dead
bacilli causes the formation of agglutinins. The power of causing
agglutination may remain in the serum for a long time after the
infection is past.

We cannot say what agglutinins are, but we know that they are
resistant, that they withstand drying, light, and putrefaction and a
considerable degree of moist heat (62° C.); like antitoxins they may
be present in normal serum; the fact that they are not effectively present
in foetal blood or in the first years of childhood gives weight to the
supposition that they may be caused by "subinfection."

Agglutinins, it may be briefly stated, are not the same as precipitins,
nor are they bacteriolysins (bodies that cause the destruction of bacteria).
It is further evident that one organism can give rise to more than one
agglutinin, and in the case of bacteria that are related to one another,
some of these agglutinins are the same—"group agglutinins." We think,
therefore, that a species of organism can give rise on the one hand to an
agglutinin that is specific to itself, and to others that are also capable
of being formed by other related organisms. Thus bacillus I can lead to
the production of agglutinins A, B, C, D, and E, whereas bacillus II can
form D, E, F, G, and H, and so on. The nature of the agglutination
process is probably that the agglutinins bring about an alteration in
the molecular attraction or tension between the bacteria and the fluid
medium. We would correlate with this the gathering into rouleaux of
the blood corpuscles, and the physical experiment in which matches
(to represent bacilli) or disks of cork (to represent red-blood cells) are
coated with hard soap and floated in a tub of water; they float about

free till the water is faintly acidulated, and then they gather together into clumps; if the water be rendered alkaline, the clumps if broken up do not re-form. First, there is probably a junction between the agglutinins and the bacterial cell, and as a consequence a physical change is wrought in the medium in which they lie and in the surface tension of the bacteria, a change with which the salts are concerned.

Cytolysins.—The blood of one person injected into the body of another may lead to the dissolution of corpuscles of the latter individual or to coagulation in his vessels. If an animal A be inoculated repeatedly with small amounts of the blood corpuscles of an animal B of another species, within a few days the blood serum of A gains the power of "laking" the blood of B, that is, of destroying the red-blood cells of it with liberation of the hemoglobin. The injection of the corpuscles leads to the formation in the blood of A of a cytotoxin or cytolysin. When this was discovered, a series of similar lysins were determined, including **leukolysins**, which are made by the injection of leukocytes, the leukolysin being specific for the kind of leukocyte introduced. Similarly, **nephrolysins** and **hepatolysins** were discovered, able to set up degenerations in the kidney and liver cells respectively; in fact, the cells of every organ seem to have their specific lysin able to act especially upon that organ. The destructive effect is most marked when the animals used are of widely different species, in which case the lysins are called **heterolysins**, but there is some interaction even between animals of the same species (**isolysins**). But it is not possible to manufacture experimentally **autolysins**, that is, substances derived from an animal which can break up its own cells. This observation is in keeping with the impossibility of making anti-enzymes to the common enzymes of the body. Before leaving this part of the subject it is necessary to note that while a cytolysin acts most powerfully upon the cells of the special kind which constituted its antigen, and in reaction to which it was produced, it may have a certain lesser effect upon other cells, and this is not wonderful when we consider the common origin of the cells of the body and the likelihood that they will, therefore, have certain qualities in common. Just as occurred with precipitins, if cytolysins be cautiously injected anti-cytolysins can be obtained, and these will neutralize the action of the cytolysins.

The Mechanism of Cytolysis.—If a guinea-pig has rabbits' corpuscles injected into it, its serum quickly becomes active in breaking up the rabbits' corpuscles, and is then called **immune**, but if we heat it to 55° or 60° C. the hemolytic action is arrested, and such serum is said to be **inactivated**. If we mix rabbits' corpuscles and heated (**inactivated**) guinea-pig serum (which calls forth no hemolysis) and add to it **normal** guinea-pig or rabbit serum hemolysis does take place. This means that heating the guinea-pig's serum has destroyed something which the normal serum can restore or that there is something present in unheated immunized guinea-pig serum and again something in normal serum that is necessary to hemolysis. There must be more than one

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body present, because non-immune guinea-pig serum is not able by itself to produce the effect. *In every case of cytolysis the existence and combined action of these two factors can be shown.* The substance developed in the serum of the immunized animal is called the **immune body** or the **intermediate body** or **amboceptor**; and the body present in the normal (and in active immune serum) is the **complement** or **alexin**. Both are present in the cytolytic serum, and in fact it is by virtue of their presence that the serum is cytolytic. From experiments we deduce that the immune body can attach itself to the cell, but cannot disintegrate it, while the disintegration is done by the complement acting with the immune body. Graphically we express this by Fig. 41, in which it will be seen that the immune body is imagined as capable of a double attachment, hence the name amboceptor,[1] to complement on the one hand and to cell on the other. Nor must it be thought that complement and amboceptor are merely theoretical names, for each has a definite existence and is as real as if it were a chemical enclosed in a bottle and visible to the eye. Further, in the interaction of complement, amboceptor and cell, an exact amount of each is necessary for a perfect reaction; an excess or lack of one or another leads to an imperfect reaction.
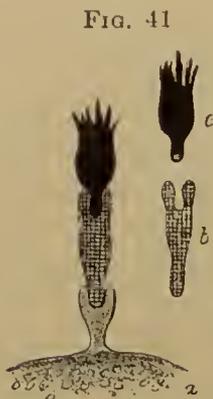
Fig. 41

Combination of cell *a*, amboceptor *b*, and complement *c*. The amboceptor may unite with the cell, but by itself cannot effect it. The complement cannot unite with the cell except through the amboceptor, having no adaptation to the cell directly.

The Existence of Different Kinds of Amboceptors.—If a goat be doubly immunized to both guinea-pigs' and rabbits' red corpuscles and this goat's serum be used upon guinea-pigs' corpuscles until no further hemolysis can be obtained, we find that there are yet amboceptors in it capable of hemolysing rabbits' corpuscles; the goat's serum thus contains two distinct sets of amboceptors, and many other such experiments lead us to deduce that there is a multiplicity of immune bodies (or amboceptors).

The Existence of Different Kinds of Receptors.—It follows from the last statement that the cells must have multiple "couplers" or receptors, and while each cell may have a large series of these, the series is not an identical one for the cells of different individuals of the same species; for example, if we inoculate a goat with serum from another goat, the serum obtained from it will hemolyse the corpuscles of some but not of all goats. We may express this graphically by saying that if goats' corpuscles are capable of having a full series of receptors, *a*, *b*, *c*, *d*, *e*, *f*, and we use for experiment a goat whose cells have receptors *a*, *b*, and *c*, its serum will come to contain amboceptors for *a*, *b*, and *c*, but not for *d*, *e*, *f*. If this serum with amboceptors *a*, *b*, and *c*, come in contact with goats' corpuscles possessing receptors *a*, *b*, and *c*, it will

[1] *Ambo*, both; *capio*, I seize.

destroy them wholly; but if with corpuscles possessing receptors *a* and *c*, it will only partially destroy them; if with corpuscles possessing receptors *d*, *e*, and *f*, it will have no effect on them.

The Existence of Different Kinds of Complements.—Much debate has taken place upon the question whether in a given blood different complements exist, and without recapitulating the lengthy evidence we may state that it seems likely that there is multiplicity of complements. We may say that *there is in every normal serum a series of complements*, and again that, *in different animals there exists a certain number of identical complements*, identical at least in their haptophore (or coupling) parts, although the toxophore (or destructive) part may be different. Just as was the case with the toxin molecule, so the complement may be imagined as of two parts; just as the toxin could be modified to a toxoid, so the complement may be modified to a **complementoid**, which will still have its old affinities but will have lost its cytolytic powers; still, such altered complement can join with the immune body, and the toxophoric or cytolytic part being powerless, no damage to the cell results, but other and active complement is prevented from joining.

Lastly, it may be pointed out that the amount of complement present is a variable quantity, and it may by various experimental means and by disease be reduced, or may, by the injection of substances like blood plasma and broth, be increased.

Bacteriolysins.—As inoculation of animal cells leads to the production of bodies causing the destruction of those cells, so has the inoculation of vegetable cells, bacilli for example, a like result; thus to obtain perfect immunity *against bacteria which develop endotoxins*, two distinct processes have to be carried out: (1) the development of bacteriolysis whereby the endotoxins become liberated, and (2) the formation of anti- (endo) toxins. Nor is it by any means easy to attain these two results; it not infrequently happens that having gained the first, a dose of the living germs will cause death in a relatively short period; the bacteriolytic power that has been acquired, destroying the bacteria, liberates rapidly so large a quantity of endotoxin that the animal dies of intoxication. To combat such an endotoxin, it is necessary to employ a method different from that used in neutralizing a diffusible toxin. If, for example, a guinea-pig by successive injections of one of certain pathogenic organisms be rendered immune, and what would ordinarily be an abundantly fatal dose of that organism be injected into the peritoneal cavity, it will be seen by removing peritoneal fluid from time to time that the bacteria are undergoing destruction, and this apart from the process of phagocytosis; the bacteria are seen to become motionless, to swell, to become rounded and then melt away by a process of gradual diminution, like a grain of sugar in water (**Pfeiffer's reaction**). What is happening is that the immunization of the animal has produced amboceptors and the normal serum supplies complement, and the bacteriolytic effect is produced upon the bacterial body.

The amboceptors and complements both constitute antibodies, and

exist in the serum, and even in the plasma of normal animals, although not in large amounts; inoculation by a specific germ is needed to call forth amboceptors abundantly; the amboceptors, as we have said, are multiple, as appears from the fact that an animal immunized against cholera and typhoid provides a serum that will destroy cholera, and subsequently also typhoid organisms. The appearance of the amboceptors is not immediate, but occurs after the lapse of several days; once there, however, they may exist in the serum for a long period, even for more than a year in some cases, and when they disappear, a relatively slight inoculation of the specific organism suffices to produce them in abundance. They can be produced by successive inoculations of the living or by larger doses of the killed germs and in this way immunity may be obtained against cholera, plague, typhoid, and streptococcus infections.

When the complements come under consideration, it is seen that those of different animals are not identical, and, therefore, the immune serum of one animal will not necessarily protect another; when one adds to this that the amount of complement is reduced in disease we can partly understand failures to immunize, and can foresee that mixed immune sera will have a better chance of being efficient than the immune serum of one animal; further, human serum is most likely to afford the right order of complements for human patients, and a relatively small amount of human serum contains enough complement for a large bulk of amboceptors.

Diversion and Fixation of Complement.—Diversion of Complement.—We have already called attention to the fact that for proper immunization there must be no excess of either amboceptor or complement. If a suspension of bacteria be made in a normal serum, which has been found to contain sufficient complement to cause bacteriolysis when a known amount of inactivated serum is added (an amount containing say x amboceptors), then if ten times this amount be added, instead of bacteriolysis being hastened, it may be wholly arrested. This is explained as being due to "diversion of the complement," and it is supposed that the excess unattached amboceptors have a greater affinity or attraction for the complement molecules than have those amboceptors that have become partially satisfied by attachment to the bacteria, or, conversely, that the avidity of the bacterial receptors is greater for amboceptors, pure and simple, than for the amboceptor plus complement.

Fixation of Complement.—We owe to Bordet the observation that sensitized red corpuscles (*i. e.*, corpuscles which having been previously placed in immune serum have taken up amboceptors from the same) when placed in normal unheated serum take up all the complement present in that serum, so that now this serum becomes wholly inactive for bacteriolytic or cytolytic purposes. Bacteria similarly sensitized act in the same way, fixing all the complemental substance present in normal serum. It is evident that the amboceptor-laden cells absorb

or render inactive much more than the amount of complement necessary for the cytolytic process, and absorb or fix indifferently all orders of complement. Gengou expanded these observations, showing that a like fixation of complement takes place under conditions in which the complement is not an essential for the main process. He found, in short, that any serum in which antigen and antibody undergo union, has any complement that it contains rendered inactive.

The Wassermann Reaction.—If this be so, then the determination whether in a given serum the complement has become fixed or not, renders it possible to determine the presence or absence of either antigen or antibody in a given fluid. If either of these be present, then the addition of the other, in the presence of complement-containing serum leads to the fixation of that complement. If the complement does not become fixed, we can conclude that antigen or antibody respectively is absent from the mixture, and we can determine this point by adding to the mixture sensitized red corpuscles. If the complement has become fixed, no hemolysis ensues; if either specific antigen or antibody be absent, the complement does not undergo fixation and hemolysis occurs. This is the basis of the now widely employed Wassermann reaction for the diagnosis, more particularly, of syphilis. The test is not a little complicated in description, but the above gives its *rationale*. Wassermann first obtained what he regarded (as we now know wrongly) as a syphilitic antigen, viz., the tissue of a syphilitic foetus. To an extract of this is added the serum to be tested, diluted and heated to destroy its complement, and normal unheated guinea-pig serum containing complement. If the serum to be tested is from a case of syphilis, and contains the syphilitic antibody, then in its union with the antigen the complement will undergo fixation. Coincidently there is prepared a mixture of washed red corpuscles of some animal, and heated (immune) serum from a rabbit which has been injected with the red corpuscles in question. If this latter mixture be added to the previous mixture and no hemolysis ensues, it is evident that the complement has been fixed; it is evident then that the suspected serum contained the syphilitic antibodies. If, on the other hand, hemolysis ensues, this is an evidence that the serum tested is negative, containing no antibodies.

However, more delicate reaction can be obtained if, in place of Wassermann's so-called syphilis antigen, there be employed the alcoholic extract of an animal's heart or other normal organ, or even soluble soaps, lecithin, or bile salts. Fixation of complement there certainly is, but the reaction is not precisely of the same order as the Bordet-Gengou phenomenon. Syphilitic blood serum is found relatively rich in globulins, and it is the combination between these and lipoids that binds the natural complement of the guinea-pig's blood present in the mixture.

Animal Venoms and Antivenins.—An extensive study of snake poisons has led to the conclusion that the raw poison contains several separate toxins, such as a hemolysin, a neurotoxin, a nephrotoxin, and so on, and that some of these attack the cells directly, while others

require the intermediation of a complement; this complement is sometimes present in the blood serum and sometimes exists in the cell that is acted upon, in which case it is known as an endocomplement. By the repeated injection of minute quantities of venom into lower animals, antitoxins or **antivenins**, as they are called, can be obtained for all the animal poisons; the best-known forms are those against the venoms of the cobra, scorpion, spider, toad, salamander, and eel.

Opsonins.—The opsonins[1] are substances in the blood serum which stimulate phagocytosis. If opsonins are not present, phagocytosis of bacteria by leukocytes occurs only to a slight extent, whereas if opsonins be present, it occurs very abundantly. For example, if a person suffering from chronic furunculosis be taken, and his leukocytes removed by centrifugalizing from his serum in which they show little phagocytic power, and added to the serum of a normal person, they take up bacteria very rapidly, because the normal person's serum contains that abundance of opsonins in which the patient's serum was lacking. The normal person's leukocytes placed in the patient's serum show scarcely any phagocytic activity, so the activity depends not upon the leukocytes but upon the serum; the substances upon which this depends (opsonins) are not readily altered by heat, and become fixed by the bacteria, not by the leukocytes. The bacterial body is in some way acted upon so that the leukocytes can subsequently ingest it; the extent of this action can be gauged by noting under the microscope the average number of bacteria ingested by a total of thirty or forty leukocytes observed, and comparing it with the number ingested by normal leukocytes in normal serum. Certain precautions are necessary in the utilization of this phenomenon. (1) The bacteria must be in an emulsion, so that individual microbes are separate and not clustered. (2) The emulsion must not be thick, lest bacteria, overlying but not in leukocytes, may appear to be actually contained. (3) The counter should have considerable training before trusting his results. (4) The same pipettes should be used for the same stage of the procedure, so as to insure accuracy of measurement.

The opsonins are considered to be protective and by their action upon bacteria are used up, so that if bacteria are added to a serum and after their removal the serum be used with a second lot of bacteria, it is inert. This last depends upon the fact that there is actually combination with or absorption by the bacteria, because bacteria so removed are found to be readily taken up by leukocytes even in an inactivated serum. Opsonins are multiple; there may be, probably is, a common one in normal serum, and specific inoculations give rise to other specific opsonins. If small measured quantities of dead cultures of Staphylococcus aureus, the gonococcus, B. coli, or B. tuberculosis be injected into an individual his opsonins are, for a short period, reduced in amount (the **negative phase**), after which they increase (**positive phase**).

Since phagocytosis is an important mode of protection of the organism

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[1] From *opsono*, I cater for.

against infection, Sir Almroth Wright, whose work drew attention to these phenomena, concluded that the relative amount of opsonins in the blood furnishes an indication of the defensive powers of the individual, and has established an **opsonic index.** This is the ratio borne by the average number of bacteria per leukocyte in the patient's serum, to the number found per leukocyte in the same emulsion with a normal serum, the latter being taken as 1.0. To obtain a normal serum it is often well to "pool" the serum of half a dozen apparently healthy individuals.

In most infections the index is found to be less than 1.0. By carefully judged inoculations of dead microbes of the sort that cause the infection it is possible to bring up the index to more than 1.0, and this is frequently coincident with a marked improvement in the patient's condition. Excellent results have been obtained in many forms of infection by staphylococcus, in certain cases of infection by gonococcus and Bacillus coli, as well as of Bacillus tuberculosis. As time progresses, the value of the method seems to increase, but there is a growing tendency to employ larger amounts of the killed microbes and to lay less stress upon the technical observation of the index and more upon the signs of reaction as they are observed clinically.

Aggressins.—As the animal cell acted upon by bacteria produces antibodies, so the bacteria on their side are stimulated to produce reciprocal antibodies, and these have been named "aggressins."

This action will be understood better if a concrete example be given. If cholera spirilla be injected into the peritoneal cavity a local infection ensues; the inflammatory fluid containing the bacteria is removed and the bacteria taken out by centrifugalizing, and the few remaining organisms killed by sunlight, heat, or antiseptics; the resulting clear fluid has no toxic effect, and can be injected into another individual of the same species with impunity. If, however, along with it a *less than fatal* dose of the spirilla be injected, death shortly ensues. There is something (aggressin) in the inflammatory exudate that has paralyzed the protective agencies of the body. The presence of these aggressins explains why the exudate produced by the local growth of a given microbe has no opsonic power; the opsonins may be present but are neutralized. Finally, it may be suggested that the aggressins are to the bacterium what the opsonins are to the animal.

By taking these into account we explain the well-known phenomenon of "exaltation of virulence" by passage through a succession of animals. The virulence of an organism does not depend only upon the production of toxins; increase of virulence does not mean increased production of ectotoxins, for a filtered culture of a virulent strain of cholera or anthrax does not produce more symptoms than does that from an attenuated strain; but if the attenuated bacilli be injected there is phagocytosis, if the virulent, none. It appears as if the virulent bacilli excrete or discharge substances which are not toxins, but which have an inhibitive or "anti" action upon the body cells, substances which do not necessarily combine with the body cells to destroy them, but either neutralize the

opsonins or directly repel the body cells, the repulsion being greater than the attraction exerted by other bacterial substances.

Anaphylaxis. — **Sensitization** or **allergy** is a phenomenon connected with the injurious effect that is occasionally wrought by serum—the so-called "serum sickness" and "serum death." From the early days of the employment of antidiphtheritic serum, there have been occasionally reported cases of death following suddenly the injection of the serum. Collapse, unconsciousness, and convulsions have occurred, death ensuing with startling suddenness. Less severe symptoms, the urticarial rash, with or without systemic symptoms of lack of well-being, and other milder manifestations following the use of serum, are familiar to all. These untoward effects are produced not by the toxins or antitoxins but by the serum, and it may be said, by the way, that the risk of these is the price mankind has to pay for the blessings of serum therapy.

Again we shall illustrate this phenomenon by a concrete example. If 5 c.c. of a foreign serum be injected into a guinea-pig there are no immediate effects, and the animal becomes soon immunized to that serum. But, if instead of 5 c.c., as little as $\frac{1}{100000}$ c.c. be given, and twelve days later a second injection of 5 c.c. be given, the guinea-pig will almost certainly die, and that quickly. Instead of being rendered immune, the opposite result has been obtained; the animal has been "sensitized," and this process of sensitization is *anaphylaxis* in contradistinction to *prophylaxis*. In herbivorous animals the same result can be gained by feeding with the serum, and the blood of the sensitized animal comes to contain a substance which, when the blood is injected into other animals, sensitizes them. In man and omnivorous animals a single dose sometimes has the effect that the two doses possess in herbivorous animals, and thus serum death may occur. A possible explanation of this antecedent sensitization is suggested by the observation that whereas guinea-pigs normally show no symptoms as the result of a first dose of horse serum, after being kept for some days in a stable, a like dose results in the rapid production of anaphylactic shock. In other words, by previous exposure to most minute amounts of even volatile emanations from a particular species, animals of another species may become sensitized.

This sensitization appears at first to be opposed to our general ideas of immunity, but we have attempted to show that it is not necessarily so. As shown by Vaughan, the bacterial proteins can be split up into a poisonous and a non-poisonous portion; the same is true even of egg albumin, and its poisonous portion kills an experimental animal just as does the poison of a pathogenic bacterium. The same is true, also, of most vegetable proteins. One may sensitize an animal with the poisonous portion, or with whole albumin, but not with the non-poisonous portion, that is, the cell substance has affinity for the non-poisonous part, and forms and discharges receptors suited to this non-poisonous part. Still referring to egg albumin for illustration, ten

or twelve days later when the cells are habituated to the non-poisonous part, if we inject whole egg albumin, the cells with their excess of receptors attract the non-poisonous portion of the serum to which they are accustomed and set free the poisonous portion in the circulation,[1] which acts upon the organism and produces death. The second dose must be large enough to supply a fatal dose of the poisonous part after splitting up. It seems, further, that the poisonous portion has a special affinity for certain cells, and it is this local, rather than general, action that explains the anaphylactic phenomena. In the guinea-pig, for example, as shown by Auer, the fatal result is due to direct influence upon the plain muscle fibres of the bronchi, causing a spastic contraction with arrested respiration. In other animals also it is plain muscular fibres that appear to be specially implicated. Dale has elaborated a singularly delicate test for the existence of anaphylaxis, depending upon the reaction of plain muscle fibre. If the blood be washed out of a normal guinea-pig, and the uterus be removed and suspended in warm Locke solution, the organ shows slow periodic contractions. If horse serum or other foreign proteid be added to the Locke solution it has no effect upon the uterus. If, on the contrary, the guinea-pig has previously been sensitized, the addition of even one millionth part of volume of the horse serum or specific proteid causes an immediate intense contraction of the uterine muscle. What is true of the egg albumin is true of the protein-containing horse serum, which forms the basis of the antitoxic sera of commerce.

This does not explain why a small dose sensitizes while a large one does not; and here we must go farther, and remind the reader of what is called the dissociation of ions; if a minute quantity of salt be put into a large quantity of water it is dissociated into its Na and its Cl ions, whereas, if a large quantity be used it remains as an NaCl molecule. Similarly, the minute dose of protein may be dissociated into its poisonous and non-poisonous parts, of which the former is in quantity too minute to produce any symptoms, and the cells are able to react only to the latter. If the preliminary dose be large, the dissociation does not occur, and the body cells become accustomed to the whole protein molecule; the poisonous action is thus expended upon the cells, where its effects are not so serious as when it is free in the circulation.

It may be recalled that in our chapter upon predisposition (p. 114), attention has been called to the similarity between certain cases of idiosyncrasy, asthma, hay fever, etc., and these anaphylactic phenomena.

THEORIES OF IMMUNITY

Everyone who is in the slightest degree familiar with medical literature knows that the amount of material given out upon the subject of immunity in the last few years is mildly described by the word stupendous. It is evident that we can give as briefly as possible not an

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[1] The *anaphylotoxin* of Friedberger.

indication of the various arguments in favor of various theories, but only a very brief explanation of a single practical one. We shall attempt to outline a workable plan by which immunity can be understood, based largely upon Ehrlich's views.

We have seen that all the substances that can induce the production of antibodies (*i. e.*, all **antigens**) are either cells or the products of cell activity, and that the antibodies, too, are the products of cell activity, and that one group is a kind of looking-glass reflection of the other. If we were bacteria we would regard the antibodies as toxins, and our own toxins as protective antibodies. Two living organisms, the animal and the microbe, are pitted against each other, and the increase of virulence of the latter may be the result of its developing anti-anti-toxins (which, from the microbe's point of view, are simple antitoxins), corresponding to the development of antitoxins by the animal and tending to neutralize them. The problems of immunity narrow themselves down to special problems bearing upon the assimilation or digestion of unusual or foreign proteid matter, the products of cell metabolism.

We have given the basis of Ehrlich's theory referring to simple toxins, but when we reach the cytolysins we are met by a new phenomenon in which there is not simple union of the molecule of the cell and the toxin or the complement, but where this is brought about by the intervention of an intermediate body or amboceptor. We may here recapitulate the various forms of antigens and antibodies with which we have dealt:—

Enzymes	.leading to the production of		Antienzymes
Phytotoxins	"	"	Anti (phyto) toxins
Bacterial ectotoxins	"	"	Antitoxins
Animal venoms (simple) . . .	"	"	Antivenins
Animal venoms (complex, requiring intermediation of complement for action)	"	"	Antihemolysins, etc.

Toxenzymes setting up production of proteid antibodies.

Proteins { animal / vegetable }	"	"	Precipitins
Bacterial proteins (?)	"	"	Agglutinins
Bacterial aggressins (?)	"	"	Opsonins

Acting singly.

Vegetable cells (bacteria)	"	"	Bacteriolysins
Animal cells of various orders . .	"	"	Cytolysins
			Hemolysins
			Leukotoxins
			Hepatolysins, etc.

Requiring interaction of 1 amboceptor (specific), 2 complement (non-specific)

Reviewing this table, one notes that there is a progression from a simple structure of the absorbed body to a very complex one. According to the nature of the body to be absorbed, the binding apparatus must differ. To tie a simple substance to the biophoric molecule we may presume that a single, simple side-chain is enough. When, however, we come to the giant molecule of a protein, this will not be enough. Giant molecules, as such, are useless for the cell, and must be broken up, dissociated, by fermentative processes. This could be if the "seizing arm" were of a nature complex enough.to seize the molecule and

to bring into contact with it the requisite ferment; to borrow an example from the vegetable world, the tentacles of the Drosera seize the object, and cover it with a juice that is digestive. Such a complex side-chain we can predicate in the case where the body to be "lysed" consists of complex proteins, such as we find in bacteria, in blood corpuscles, or in cells. If there be such a complex side-chain, the process of immunization will cause a reproduction of such side-chains, and the side-chain with its complexities will be elaborated and cast off as a complete whole—as an immune body.

FIG. 42
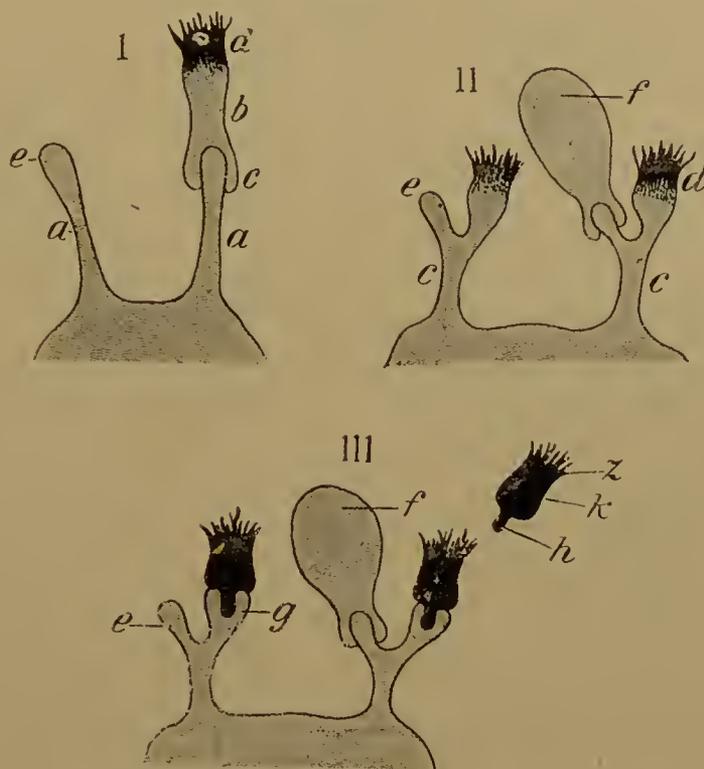
The three orders of side-chains, according to Ehrlich.

Ehrlich's Three Orders of Receptors.—Following up this idea, Ehrlich supposes that there are three orders of receptors for food or toxin molecules. (1) The simple toxin (*I*, *b*) is anchored by a receptor (*I*, *a*) of the first order, that receptor being a side-chain with a haptophore *e* to which the toxin molecule becomes coupled by its haptophore *c*. (2) For protein molecules, a different order must be imagined. The side-chain must have an arm for seizing (*II*, *e*) and one (*II*, *d*) for supplying the ferment by which the molecule must be dissociated, that is, a haptophore and a **zymophore** (or ferment-carrying portion). This kind of receptor is figured in Fig. 42, *II*, in which *e* is the haptophore, *d* the zymophore; as soon as coupling occurs, the zymophore is free to exert its ferment effect upon the body seized. It will be seen that the toxin molecule in Fig. 42, *I*, is the counterpart of the attached receptor of Fig. 42, *II*. (3) For the yet more complicated case of an interaction between the biophoric molecule and a foreign cell, we must presuppose a complex receptor as in Fig. 42, *III*. The receptor must

be capable of attaching the cell to be acted upon (*f*) and the complement (*k*); the complement is figured as possessing a haptophoric part
(*h*), and a zymophoric part (*z*), which latter corresponds to the toxophoric part of the toxin molecule. When both these are fixed to the
original cell, the communication between the zymophoric part and
the two cells permits the enzyme action upon the attached cell (*f*) to
begin. When the cell receptors are produced in excess and discharged,
they have the same powers of attachment as when fixed to the biophoric molecule and when free are termed by Ehrlich **haptines**. Haptines are thus of three orders, those with a single haptophore, such
as antitoxins and anti-enzymes; those with a haptophore and a zymophore group, the agglutinins and the precipitins, and lastly, those
with two haptophores, which are the amboceptors or immune bodies
proper, and constitute the cytolysins and bacteriolysins.

There is a word of warning to be given to the beginner in interpreting the diagrams which we have reproduced. We are not sure
that the toxin molecule becomes anchored on to the biophoric molecule
and so becomes a part of it. The interaction of toxin on haptine is
direct: the toxin acts upon the biophoric molecule in a way that is
less direct; we differ from Ehrlich in not regarding it as becoming
firmly attached to the biophoric molecule, but as dissociating, by its
affinity, the receptor, the toxin and receptor becoming temporarily a
free unit, and imagine that thereby the condition of unsatisfaction, in
which the biophoric molecule is left, leads to the formation of a new
side-chain or receptor.

When we consider the processes by which bacteria are destroyed,
and their cell products neutralized we realize that these are but special
examples of assimilation and digestion. The process by which an
ingested microbe is dissolved in the vacuole of the leukocyte, or a bacterium melted in the body fluids is probably brought about by a procedure of the same order as when fibrin is digested in the gastric juice.[1]
In no part of the whole subject can we neglect the importance of enzyme
action. We readily admit—nay, we cite—the different grades of
enzyme action with which we are familiar; how ptyalin acts directly
on starch, and enterokinase requires the mediation of trypsinogen.
We think, in short, that toxins and cytolysins are of enzyme nature.
Indicating the similarity between toxins and enzymes, we have antitoxins and anti-enzymes, we have natural and experimentally acquired
anti-enzymes just as we have actual and experimentally acquired antitoxins, we have evidence that a minimal amount of enzyme may convert
a maximum amount of the substance acted on, and a minimal amount
of toxin cause dissociation of the cell substance, even unto death, or
that, under favorable circumstances either process may be arrested;
we see, too, that the action of both is arrested by the products of

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[1] Or perhaps, more accurately, in the pancreatic juice, for such digestion is lytic
and we now recognize that for the activation of the trypsinogen a second body is
necessary. Trypsinogen is inert save in the presence of enterokinase, which may be
regarded as the complement, the trypsinogen as amboceptor.

dissociation; both work with chemical exactitude, so much enzyme neutralizes so much anti-enzyme, and so much toxin so much antitoxin.

We do not know the structure of enzymes or of toxins, and we must, therefore, express the process by symbols as Ehrlich has done. If we are speaking of enzymes, the enzyme molecule (corresponding to the toxin molecule of our previous illustrations) has a haptophoric (coupling) part, and a zymophoric part, and instead of the cell body we have this time the substance to be fermented (the fermentescible substance). Now let us digress to the consideration of the chemistry of fermentation; for example, dextrose gives rise to glucose thus:

$$C_{12}H_{22}O_{11} + E + H_2O = C_6H_{12}O_6 + C_6H_{12}O_6 + E.$$
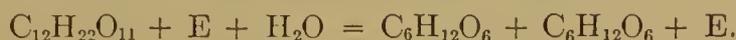
One molecule of dextrose $+ H_2O =$ two molecules of glucose. In the presence of enzyme (E) hydrolysis occurs.

The molecule of dextrose cannot be split into two equal parts, but divides unequally, thus:

$$C_{12}H_{22}O_{11} = \begin{cases} C_6H_{11}O_5 \\ C_6H_{11}O_6 \end{cases}$$
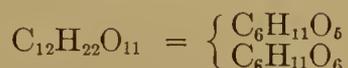
and the hydrolysis gives us a free basic HO ion, and a free acid H ion. The next step is that we expand our last formula thus:

$$C_{12}H_{22}O_{11} + H_2O = \begin{cases} C_6H_{11}O_5 + OH = C_6H_{12}O_6. \\ C_6H_{11}O_6 + H\ \ = C_6H_{12}O_6. \end{cases}$$

The dextrose molecule splits into two parts, one of which has positive, the other negative affinities, and when these are separated one attracts a basic ion, the other an acid ion. Our conception is that the enzyme which thus splits up the molecule into a basic and an acid part, must itself be acid or basic; thus, if acid it detaches the basic complex $C_6H_{11}O_6$, but the hydrolysis has left free an H ion, which now exerts a greater attraction for the $C_6H_{11}O_6$ than does the enzyme; the two combine, and the enzyme is set free to break up another molecule of the dextrose. We have indicated this graphically in Fig. 43, the term recipient indicating the substance (in this example *G*) which has affinity for the broken-off molecule, greater than has the ferment.

In more complicated enzyme action such as occurs in the protein-splitting digestion of trypsin, the enzyme is a compound of kinase and trypsinogen; the latter has a suitable haptophore group, but its zymophore group is unable by itself to split the protein molecule and requires the assistance of the kinase.

When we liken the action of enzyme to that of toxin, we recognize that there is a frequent source of confusion in the conception on the part of the worker that enzyme action results ordinarily in the production of substances which are certainly not anti-enzymes, and there appears at first sight to be no similar action on the part of toxin molecules. These, we are apt to imagine, produce only antitoxins. This, however, is a mistaken idea. The process of junction between toxin and antitoxin is associative and self-limiting, and there is an identical

process occurring between enzyme and anti-enzyme. What we wish specially to point out is that, corresponding to the process manifesting itself between ferment and fermentescible substance which is dissociative and recurrent, there is, we hold, an exactly parallel dissociative

FIG. 43
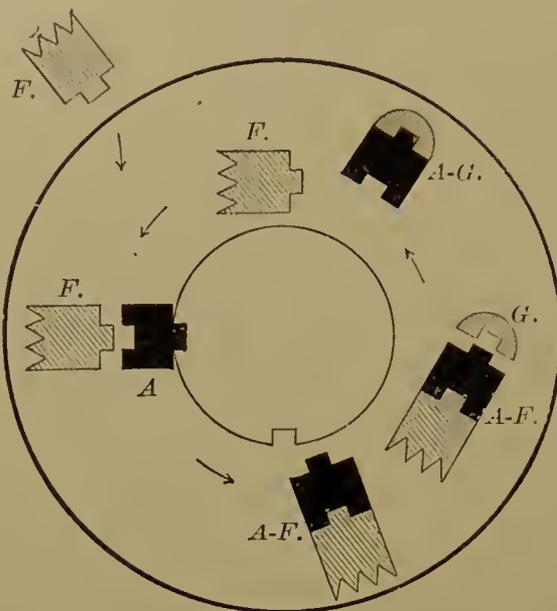
Simple enzyme action: *F*, the enzyme molecule, has affinity for and detaches *A*, a side-chain of a protein molecule, forming a temporary combination with it. When *A–F* is free the recipient *G* has a greater affinity for the side-chain moiety *A–F* and combines with it, the enzyme molecule *F* becoming detached and ready to dissociate a second similar side-chain.

FIG. 44
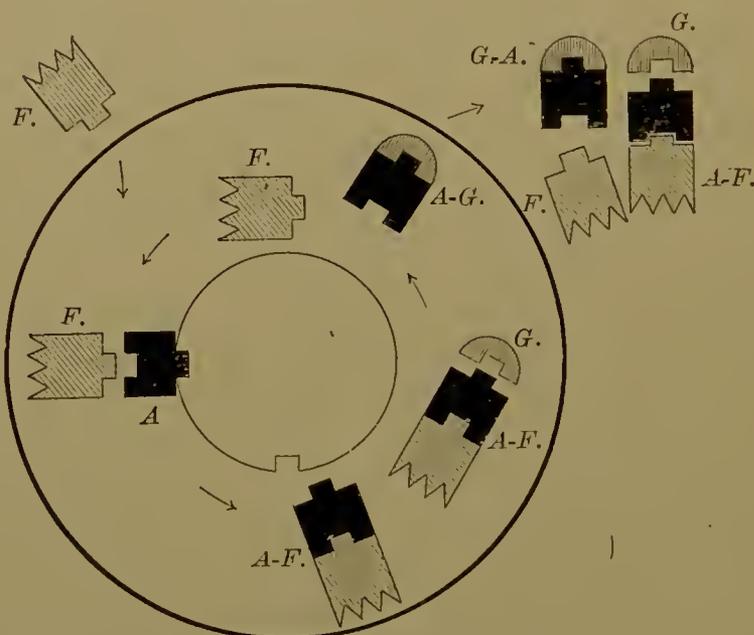
Schema of toxin-antitoxin action: *G–A* (the side-chain *A* combined with the recipient *G*, as in Fig. 43, when discharged from the cell into the surrounding fluid as an antitoxin molecule, is dissociated by the enzyme or toxin molecule *F*, which thus joining with *A* becomes neutralized.

and recurrent process occurring between the toxin and the biophoric molecule. The one essential difference is that the enzyme may manifest this dissociative activity *outside* the cell, the toxin can manifest it only within the cell and in association with living matter.

It is when the enzyme acts upon the living cell that anti-enzymes are produced, just as antitoxins are developed under like circumstances. And to explain the relationship between the fermentescible or dissociative and the antibody or associative activities of both orders of substances, we suggest an addition to Professor Ehrlich's conception of side-chain activities. In toxins and antibodies he takes no note of the group of junction with the biophoric molecule; when dissociated, there must be here in the side-chain complex (which in our diagram, Fig. 44, is solid black) a satisfiable affinity. If now we picture the toxin molecule, not as becoming attached to the biophoric molecule by one of the side-chains of the same, but *as detaching the side-chain*, we can solve the difficulty; that is, we can regard the toxin as acting like an enzyme, detaching the side-chain, giving it up to the stronger affinity of the recipient *G*, and being free to detach another side-chain. *This side-chain plus recipient is the antitoxin* (Fig. 44).

In the cell this antitoxin cannot act because the toxin has affinities for the similar side-chains of the biophoric molecule still adherent, unless the point is reached at which equilibrium occurs by the accumulation of the products of the enzyme action and by the overproduction and discharge of side-chains of the particular order into the paraplasm. But when the excess of side-chains plus recipient is discharged into the blood stream, then circulating toxins, not having the greater attraction of the intracellular molecules, are free to join them and be neutralized.

In this consideration of the subject we have called in no external factor save the "recipient," some simple but active ion present in all solutions in which the enzyme or toxin is able to act.

These views as regards the reaction of the body to bacteria and their toxins being but modifications of the digestive process, and the enzyme-like nature of toxins, have constituted our teaching for many years. Of late they have gained strong support from the observations of Vaughan, Abderhalden and Friedberger upon the dissociation of proteins and anaphylactic phenomena. Stated briefly these recognize two broad groups of phenomena: the reaction of ectotoxins and foreign enzymes on the one hand, the reaction to bacterial and other cell bodies, to foreign proteins, on the other. The cells and tissues react to the former by elaborating and throwing off protein substances which, uniting with the enzyme-like bodies, form relatively stable inert compounds. They react to the latter by elaborating lysins, proteolytic *enzymes*, whereby these foreign proteins become dissociated, digested, and converted into foodstuffs. In this process of adaptation to the foreign proteins, or immunization, two stages are to be recognized. In the first or incomplete stage "lysins of the first order" (Gurd) are elaborated, possessed of only an imperfect splitting up capacity. It is these lysins of the first order that, on the one hand, are responsible for the symptoms of infectious disease, on the other for the phenomena of sensitization or anaphylaxis. According to these views bacteria such

as the typhoid bacilli, which give off no ectotoxins, are in themselves harmless and inert so long as they are not taken up and digested by the cells. As already indicated (p. 142) the period preceding such digestion constitutes the incubation period. A certain time—usually several days—is requisite before the cells gain the power of dissociating the foreign proteid. This dissociation at first splits up the proteins of the bacterial body into a relatively inert, or non-toxic, and into a toxic moiety. It is the toxic moiety liberated in extraordinarily minute amounts at any one moment that, diffusing, causes the symptoms of disease. It is this same toxic moiety which in a sensitized animal liberated in greater bulk upon the introduction of the second dose of a foreign protein induces the phenomena of anaphylaxis. It is the production of these poisonous disintegrative products which characterizes thus the second stage of immunization. Anaphylaxis therefore represents an intermediate stage in the production of immunity. Complete immunity, according to this theory, is brought about by the development of "lysins of the second order" through whose intermediation the bacterial and other proteins are further dissociated, so that they give origin to foodstuffs only, without simultaneous formation of toxic substances. In harmony with these views it may be noted that whereas the incomplete products of protein dissociation, such as the peptones and proteoses, are definitely toxic when introduced into the tissues, the amino-acids and other products of more complete dissociation are in general harmless.

Thus to epitomize, antitoxin and anti-enzyme formation is the production by the organism of specific proteins capable of neutralizing the toxins and enzymes, whereas in cytolysis, hemolysis and bacteriolysis the organism on the contrary develops specific enzymes for the purpose of dissociating foreign proteins.

PAIN

Pain is the cry of the tissues. The infant cannot explain its discomforts and expresses them by crying; equally the tissues have no means of expressing to the individual that something is wrong, save by the presence of the sensation that need not be defined because universally experienced—pain. Paradoxical as it seems, pain cannot exist in the tissues; a pain in the foot is a disturbance of those nerve cells in the brain whose function is to receive stimuli conveyed to them by the afferent nerves from that region.

In this connection we must recognize two orders of tissues, irritation of either of which may set up the sensation of pain, but in the one this process is accurately localized, while in the other the sensation is localized by the brain as originating in some other area or areas. Of the former may be mentioned the skin, the mucous membrane of the mouth and pharynx, the skeletal muscles, the periosteum, and the tunica vaginalis of the testis; of the latter, all the viscera, with the

exception of the testis, or more accurately, of its serous coat. This may seem to be a sweeping and unfounded statement and one contrary to personal experience, but as a matter of fact, the individual viscera may be handled with impunity and even be cut in the unanesthetized individual without any sensation being induced. In such organs there are no sensory nerves for pain, no direct paths whereby the consciousness is informed of disturbance in those particular viscera. Stating this, we do not mean to indicate that pain may not originate from the viscera; every schoolboy knows a stomach-ache as a very real thing, and undoubtedly a dull heavy pain follows pressure or serious traction upon these viscera, though here again we are unable to localize the pain in any particular area. At most we have an obscure realization of something wrong inside. When, for example, the œsophagus or stomach, or the colon is overdistended, there may be painful sensations behind the sternum, in the upper or lower abdominal areas respectively.

If we analyze the pain associated with disturbances of the internal viscera, we encounter some points of remarkable interest. Take for example, the organ just noted—the stomach. An ulcer or other acute lesion of this viscus is found to afford a pain which, if the patient be asked to localize it, is situated *in the abdominal wall* in the epigastric region. We may even observe that if the lesion be in the cardiac part of the stomach, the pain is in the upper part of this region, if toward the pylorus in the lower, and this irrespective of the fact that the cardiac and pyloric regions lie somewhat transversely, rather than vertically one above the other. In addition, the patient endeavors, and if he be at all stout, endeavors in vain, to touch an area in the dorsal region between and rather below the shoulder blades; more accurately on either side of the seventh and eighth dorsal vertebræ. With the heart, as, for example, in angina pectoris where the pain is extreme, it is noteworthy that it is complained of as existing, not in the organ itself but over it. There is frequently felt also a sense of extreme constriction along the line of the second rib, and with this, further, a pain extending down the inner side of the left or occasionally the right arm, or both, most often as far as the elbow, and occasionally as far as the little finger and the ulnar side of the ring finger.

It is to English-speaking observers more particularly that we owe the study and elucidation of these so-called **referred pains**. Hilton, in his well-known lectures on "Rest and Pain," published in 1863, had a very clear realization of their existence; their full study, however, we owe to James Ross, Dana, James Mackenzie, Head, and Hertz.

Each segment of the body has in the earliest vertebrate types, *e. g.*, amphioxus, its segmental nerves, and marked as has been the evolution of the nervous system of the higher vertebrates this segmental arrangement still persists, the segments being composed of the neurones of the posterior ganglia (sensory), the neurones of the anterior horns (motor), and the neurones of the sympathetic system. Each segment

of the body has thus its system of sensory, motor, and sympathetic nerves, these latter being of both orders, sensory and motor. The researches of recent years (Gaskell, Langley, and others) have thrown much light upon the structure and functions of the sympathetic system, or, to speak more accurately, of the *autonomic* system. What we have been accustomed to describe as the sympathetic system is related only

FIG. 45
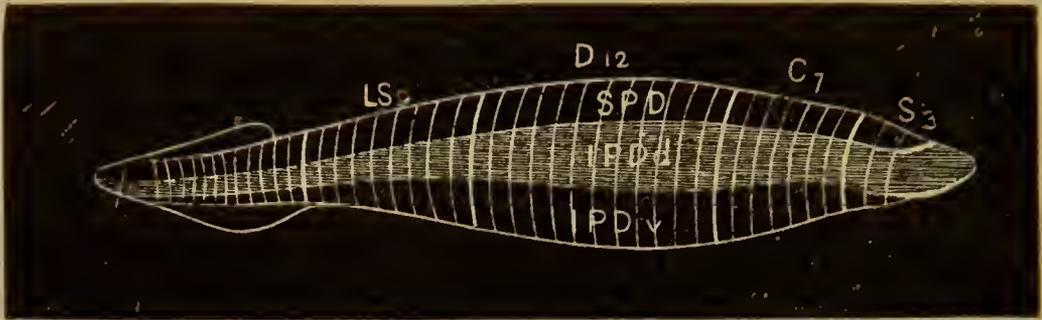
Representation of primitive vertebral animal—the amphioxus—divided for convenience into three segments for the head, seven for the neck, twelve for the dorsal, nine for the lumbosacral region, and an indefinite number for the cocceygeal region: *SPD*, the superior primary divisions of the nerves supplying the surface over the neural canal; *IPDd*, the dorsal trunks of the inferior primary division supplying the lateral surface of the body, and *IPDv*, the ventral trunk of the inferior primary division supplying the ventral surface. The parts supplied by the dorsal trunks of the inferior division are alone lined. (Ross.)

FIG. 46
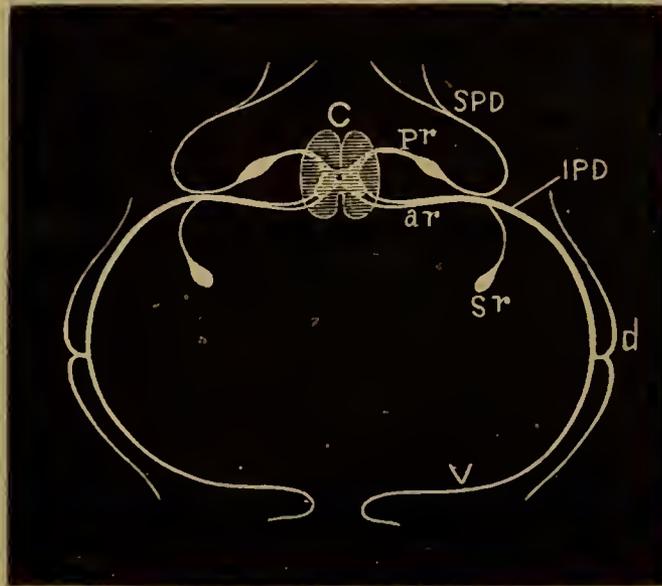
Diagram showing constitution of a spinal nerve: *C*, spinal cord; *Pr*, *ar*, posterior gangliated and anterior non-gangliated root of nerve respectively; *SPD*, superior primary division; *IPD*, inferior primary division; *d*, *v*, the dorsal and ventral branches respectively; *Sr*, sympathetic (gangliated) root. (Ross.)

to the thoraco-lumbar cord. Langley has pointed out that from the mid-brain, hind brain and sacral cord, other fibres originate which have the same remarkable arrangement of their efferent fibres. Whereas the afferent path of the cerebrospinal nerves has its cell bodies in the brain or cord, with axones which traverse without interruption the whole distance from the gray matter to the muscles innervated (the

"lower motor neurones"), in the autonomic system the efferent path always exhibits a relay. The proximal member passes from the brain or cord to end in a sympathetic ganglion where its arborizations surround the cell bodies of the distal member whose axones extend to some smooth muscle or gland, The ordinary cerebrospinal efferent nerves all innervate striated muscle.

The afferent or sensory nerves of the autonomic system are fewer, and unlike the ordinary cerebrospinal sensory nerves have no axones ascending to the brain in the posterior root zone.

In the process of development the various groups of nerves come to lie in different planes, the sympathetic motor neurones, for example, becoming grouped into ganglia, some of which, *e. g.*, the cervical, represent the fusion of the neurones of several segments. So also the superficial sensory nerves do not necessarily lie in the same plane as do the muscles supplied by the motor nerves of the same segment; every schoolboy should know, although he may not have analyzed the fact, that the region of the buttocks is supplied by sensory nerves originating from a singularly large number of spinal segments; while as regards the internal viscera such as the heart, stomach, and intestines, these with their associated nerves come to lie widely remote from their original segmental position, both actually and relatively. Thus to explain the instances given, the stomach is innervated from the level of the seventh, eighth, and ninth dorsal; this region also affords the sensory nerves which on the posterior aspect of the body supply the lower dorsal region between the shoulders and in front innervate the abdominal wall of the epigastric area, the anterior muscular branches innervating the corresponding intercostal spaces.

The sympathetic nerves of the heart are relatively abundant and vary for the different regions; thus the auricles are innervated from the fifth to eighth dorsal segments, the ventricles from the second to fifth dorsal, the ascending arch of the aorta from the third and fourth cervical, and the first, second, and third dorsal. The referred pains vary according to the part involved, and it appears also that if the right heart be involved they show themselves on the right side of the body, if the left heart, then on the left. The referred pains in angina pectoris are most frequently along the superficial area of innervation of the ventricles, notably along the superficial sensory area belonging to the second dorsal, extending also when severe into the first dorsal segment. We are accustomed to regard the auricles as the beginning of the cardiac region, and so would expect that they should be innervated from the higher, the aorta from lower segments. If, however, we study the development of the heart we find that this begins as a simple tube which becomes bent upon itself in an S-shaped manner; it is the inferior or "caudad" portion of this tube that gives rise to the eventual auricles, the superior or "cephalad" that becomes the first part of the aorta.

What happens, therefore, in those cases where pain is experienced, is that stimuli proceeding from these internal viscera to the neurones

of a particular level of the cord, do not extend thence directly to the cerebral cortex; no mechanism exists for this direct communication; but where the stimulus is above a certain grade there is an irradiation or expansion of the stimulus to other neighboring neurones which do possess this communication with the optic thalamus, and *as a consequence, the brain localizes the seat of disturbance, not in the viscus originally disturbed, but in the areas innervated by these neighboring neurones.* It deserves note that painful sensations have their seat, not as might be expected in the cortex of the hemispheres, but in the thalamus. The cortex may be cut into without giving rise to any sensation; irritation of the thalamus of one side leads to pains referred to the other side of the body, its destruction to anesthesia of that other side.

This, however, is not everything. If long continued, this segmental irradiation induces a condition of heightened irritability in these neighboring neurones, the result of which is that minimal stimuli reaching them have maximal effects, so that the areas supplied by their sensory branches become hyperesthetic; and the irradiation affects the neurones also of segments above and below, and thus not merely is the sense of pain localized in these other areas, but these other areas become the seat of actual hyperesthesia, so that now a stimulation of these areas, as by pricking or pressure or traction, gives the sensation of acute pain.[1] More than this, as has been pointed out in the discussion of inflammation, there may be a general vascular disturbance of such an area, giving a so-called sympathetic inflammation. Further, as we have already indicated, the area of cutaneous supply does not correspond absolutely with the segmental innervation of the underlying muscles. In the first place we may recognize with Mackenzie, a superficial and a deep cutaneous hyperesthesia, possibly corresponding to the differing distribution of the tactile and painful senses, of which the latter at times is found present without the former (although it seems that when superficial hyperesthesia is elicited, the deep is always present), and in addition a yet deeper muscular hyperesthesia. To give an example, where there is enlargement of the liver, the commonest pain felt is over this organ, and inasmuch as this is markedly increased by pressure, the ordinary impression is that this is an actual splanchnic or visceral pain. If, however, the area be mapped out over which pressure causes pain, it will be found to extend considerably below the edge of the liver, and if the abdominal wall be picked up over this area the muscle is exquisitely painful. There is here not a superficial but a deep muscular hyperesthesia of the abdominal wall.

We have here but touched upon the outlines of the subject, but feel that both for comprehension of disease and as an aid in diagnosis this study of painful areas is of the very first importance, even if hitherto it has not been discussed in any text-book of general pathology known to us. We would conclude by giving an indication of a few important

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[1] From which it follows that in cases of obscure visceral disturbance the mapping out of hyperesthetic zones is of prime diagnostic importance.

areas of referred pain without exact anatomical description. The
"stitch" of pleurisy is not due to the presence of sensory nerves on the
pleural surface—experiment shows that the pleuræ are insensitive—but
it is due, according to Mackenzie, to spasm of the intercostal muscles;
it is thus a referred muscular pain. None of the serous surfaces have
sensory nerves proper, with the exception of the tunica vaginalis testis.
As the testis descends into the inguinal canal, it carries before it certain
elements of the abdominal wall, the cremasteric muscle, etc., and
along with these the genital branch of the genito-crural nerve. In
those having a long cord it is easy to determine that pressure upon
the testis causes immediately acute pain localized in, or more accurately
upon the testis, and following upon this a referred pain is felt in
the groin. So also the lower end of the ureter is innervated by the
genito-crural nerve, and, *per contra*, with arrest of a stone in the ureter
there is a referred pain in the testis. We have said that the other
serous membranes are insensitive; this statement is made with a full
recognition of the fact that traction upon the peritoneum in the un-
anesthetized person may be attended by pain; but this pain, again, is
not accurately localized but is referred. We may lay down that trac-
tion upon or injury to the stomach is referred to the epigastric portion
of the abdominal wall, of the small intestine to the umbilical area, of
the large intestine to the hypogastric area. The localization of appen-
dicial disturbance is well known to be most often felt at what is known
as "McBurney's point." Irritation of the bladder, as in vesical calculus,
is characterized by pain felt in the urethra, especially at the extremity
of the penis, by reason of their common innervation by the third sacral
nerve. The rigidity which is observed in the abdominal wall accom-
panying intestinal lesions, is another manifestation of the "viscero-
muscular" reflex. Deeks has recently called attention to the existence
of a doughy inelastic skin over the abdominal wall in almost every
chronic inflammatory lesion of the abdominal viscera.

Finally, the brain itself is devoid of sensation; headache is not pain
of the brain, but, as will be recognized upon consideration, is a super-
ficial phenomenon, due to irritation to one or other of the cranial nerves,
or in the case of occipital headache, of the spinal accessory and second
cervical nerves. The brow-ache experienced after an ice has been
eaten in haste is due to the fact that the sensory nucleus of the fifth
nerve has been stimulated by irradiation, the afferent nerves of the
œsophagus being in the main vagal, and the vagus nucleus being situated
close to that of the trigeminal.

In short, to quote James Mackenzie, "the sensation of pain from
whatever source the stimulation arises, is referred to the peripheral
distribution of sensory nerves in the external body wall." This source
may be (1) in the brain itself, as, for example, where an epileptic attack,
due to cerebral irritation begins with pain in the distant part (*aura*); (2)
in the cord, *e. g.*, the girdle pains of tabes dorsalis; (3) in the posterior
root ganglia, *e. g.*, the pain of herpes zoster; (4) in the viscera, of

which numerous examples have been quoted, or (5) in the external body wall and skeletal muscles, where only (with the exceptions noted) the pain informs us of the actual seat of the disturbance.

Finally, while speaking thus broadly of pain it must be kept well in mind that there are various and distinct orders of sensory nerves, disturbance of any one order of which gives rise to the sensation of pain, namely, nerves for the tactile sense, for the muscular sense, for heat, for cold, not to mention yet other orders the existence of which is evidenced by the researches of Head and Mackenzie. We owe to Head and his experiments upon himself (by section of sensory nerves) the recognition of a more primitive **protopathic** series of sensory nerves and a series of later development affording the finer tactile and temperature differentiations (**epicritic** nerves).

SYNCOPE, SHOCK, AND COLLAPSE

We now pass to a brief consideration of several bodily states in which the prominent condition is the more or less rapid development of inanition and arrest of bodily function. At first sight these one and all appear to be due to inhibition or arrest of nervous control over the organism at large. More careful study indicates that in their origin these may be very diverse, and during the last few years the active investigations of a large body of observers have resulted in such apparently discordant results that the time is not ripe to lay down any positive teaching. These observations have been directed mainly toward the elucidation of *surgical shock* and the devising of means to arrest the profound lowering of vitality which at times succeeds operations of, it may be, only secondary magnitude, and what is more, operations, it may be, so conducted as to be devoid of pain. The skin becomes blanched, the pulse so feeble and fluttering that it is scarcely detected, the eyes sunken and cheek bones prominent (facies Hippocratica), the respiration shallow, the temperature may fall several degrees below normal, the breath become almost cold. There may be frequent retching and vomiting. The lowering of vitality is such that the patient lies limp and regardless of his surroundings: not wholly unconscious, for by shouting or strong stimulation he can be aroused, but his answers come slowly, as if brought from a distance and difficult to obtain; they are, however, rational. Volition is at a minimum, and there is extreme general depression of all bodily functions. In this state the patient may continue for many hours or even days, gradually recovering power and activity, or on the other hand the state may become more and more grave, until stimulants of no order are of influence, the respiratory efforts become far apart, and death ends the scene. Before seeking an explanation of this surgical shock, it will be well to pass in review sundry allied conditions which we can label with more or less definiteness.

1. **Emotional Shock.** This may produce sudden death. The case is cited of a mock trial conducted upon an obnoxious janitor by some

students of a Scottish university. After an impressive trial and condemnation he was led to the block, struck across the neck by a wet towel—and picked up dead.

What appears to be the natural explanation of such cases is strong vagus stimulation with inhibition of the cardiac and possibly the respiratory centres.

2. **Syncope** or fainting is the state in which the face suddenly becomes blanched, the pulse small, rapid, and at times imperceptible; a brief giddiness or a moment of mental helplessness is followed by unconsciousness, the individual falling "as a sail falls, the mast being broken." This arises in various ways: by the sudden assuming of the erect from the supine position, by the emptying of a full bladder (with probably a mechanical filling of abdominal vessels), or by strong stimulation of sensory nerves, in other words, pain. Unconsciousness is usually brief. Again, syncope may be purely of emotional origin. Many medical students will recall cases of syncope occurring among their own number at sight of some operation, especially if the surgical procedure be one that is undertaken without an anesthetic; the ready mind of the sympathetic one attributes to himself all the sensations (and more) undergone by the patient. Personal memory recalls vividly a football match, with the scattered falling, like pole-axed steers, of nearly half a score of undergraduate onlookers, consequent upon the loud, sharp snap of a leg bone of one of the players.

3. **Electrical Shock.** This also is clearly of nervous origin and of the same order as the former, due primarily to nervous stimulation. According to the intensity of the current, and the path traversed by it, it may, as in many struck by lightning, cause instant death, or as already noted (p. 69) produce arrest of heart action and respiration with apparent death from which by appropriate means there may be recovery, or again without absolute arrest of heart or respiration there may be prolonged unconsciousness.

4. **Anaphylactic Shock.** This may lead to acute death in the course of two or three minutes, or set up various grades of disturbance down to urticaria and cutaneous sensory irregularity. While as indicated by headache, photophobia and sensory disturbances the nervous system may be affected, the outstanding phenomena are brought about more particularly by the sensitiveness and heightened response of the involuntary muscle of one or other organ to the "anaphylaxin." In the guinea-pig, for example, death is due to the rapid and intense contraction of the smooth muscle of the bronchi.

5. **Collapse.** English writers more particularly have been inclined to make a distinction between Shock and Collapse, employing this latter term for conditions in which a similar if not identical train of symptoms follows the rapid loss of a considerable amount of the circulating fluid, whether by external or internal hemorrhage, or as in the "algid stage" of cholera, in acute dysentery, and in pernicious vomiting, by rapid discharge or excretion of the fluid of the blood into the alimen-

tary canal. In these cases we deal obviously with a condition of secondary cerebral anemia: the amount of the blood in the arterial system is insufficient to nourish the brain, despite the fact that, as indicated by rapid lowering of the specific gravity of the blood following upon a large hemorrhage, and the sinking in of the cheeks and orbits, the tissues become drained of their surplus lymph and thereby the amount of circulating fluid is increased. Such cases are benefited by intravenous saline injections.

6. **Acapnia.** We owe to Yandell Henderson the establishment of the fact that marked reduction of the carbon dioxide, or more accurately of carbon dioxide tension in the blood, is followed by the development of the symptoms of shock, and that, by the exhibition of CO_2 in the inspired air or otherwise, development may be largely prevented. Exposure of the viscera, in a laparotomy, and the aëration of the highly vascular abdominal organs are accompanied by exhalation of CO_2 and affords the anatomical and clinical picture of shock—filling of the splanchnic veins, lowered blood-pressure, cerebral anemia, and depressed cerebration, rapid and weakened heart action, etc., and he prevents the manifestation of this syndrome by bathing the exposed viscera with salt solution saturated with carbon dioxide. He believes that in the very act of placing the patient under anesthesia there is brought about an undue loss of CO_2, and thus he gives a physiological explanation of the good effects, noted for many years, of permitting the patient to reinhale the expired air while being "brought under."

Under which, if any, of these various headings are we to place the main mass of cases of surgical shock? Around this question an active contest is at present being waged. To us it seems that here, once more, as in the case of inflammation and of pyrexia we are forced to recognize the "dual control:" that identical symptoms may ensue from direct action of noxæ upon the tissues, and from stimulation, or inhibition, of the higher nervous centres.

Thus to take the simplest example: we have noted that syncope may be brought about either by direct emotional stimuli and their influence upon the vasomotor centres, or on the other hand by sudden diversion of the blood to the splanchnic area, as may occur upon suddenly assuming the erect condition when the vasomotor mechanism is inactive or caught napping. In both cases, whether secondarily or primarily, the blood drains into the splanchnic area, so that cerebral anemia is induced. So in the case already noted, where the emotional shock has been so great as to put the cardiac and respiratory centres out of gear, by supplying blood to the brain we can rapidly bring the condition to an end —e. g., by placing the fainting individual in a horizontal position and driving the blood out of the abdominal veins by the application of pressure over the waist or abdomen.

The vessels of the splanchnic area, or, indeed, of the liver alone, are capable of holding all the blood of the body. Normally the blood does

not accumulate in them because the abdominal wall by its tone compresses the viscera, and because of the tone or partial constriction of the visceral arteries and veins. But if from any cause there is rapid dilatation of the splanchnic vessels, cerebral anemia and unconsciousness are surely induced. This abdominal vasodilatation may be produced, *inter alia*, by a blow upon the abdomen, as in the "solar plexus blow" known to the prize-ring. Such a blow produces inhibition of the splanchnic vasoconstrictive influences, while simultaneously vagus stimulation of the cardio-inhibiting centre by causing arrest of the heart beat may aid in producing sudden unconsciousness. But also cerebral anemia may be directly induced by pressure upon both carotid arteries. In all these ways syncope may be brought about.

Anaphylactic shock, on the other hand, is a clear example of unconsciousness and even death being produced by direct tissue stimulation, and particularly by contraction of the plain muscle fibres so widely spread through the organism.

But in ordinary surgical shock there is frequent evidence of depression of tissue activity and function. The meal taken in the morning before an operation may be vomited in the evening absolutely unacted upon by the gastric juice, which in fact has not been excreted. Drugs like alcohol, ether, and strychnine capable of easy diffusion, time and again when injected are absolutely without effect, although later when the patient "comes round" they may manifest their characteristic actions. Is this due in most cases primarily to acapnia? It is difficult to believe this; and that because of the evidence already adduced of the sensibility of the vasomotor system to stimulation or inhibition along various reflex areas; and, secondly, because of the pronounced individual differences observed. Some manifest the symptoms of shock immediately after an operation, others succumb only, it may be, twenty-four hours later. It is difficult to see why carbon dioxide disturbances should show themselves at this late period, and Crile, without doubt, has reduced the liability to shock by his method of *anoci-anesthesia*, namely, by so administering local anesthetics that through narcosis of the local and lower nerve centres, stimuli are prevented, so far as possible, from acting upon the higher cerebral centres.

As to the distinction between shock and collapse, we are inclined to the opinion that this exists only in name and in mode of causation. In the latter, cerebral anemia of mechanical origin initiates the depression; in the former nervous disturbance initiates the circulating disturbance. In this respect acapnia is more closely allied to collapse, in that deficient CO_2 in the blood acts upon the higher centres in the same way as does deficient blood supply.

It is for us to weigh the probabilities in any given case, and, if in doubt, to utilize methods which will favorably influence both the central nervous system and the state of the tissues.

CHAPTER IV

ON THE MORE IMPORTANT INFECTIONS AND THEIR OUTSTANDING FEATURES

THE pathology of the infections includes not merely the gross and histological appearances of the specific lesions, but the study of the relationship between the properties of individual microbic species and the effects seen to be produced by those species in the animal, and more particularly in the human body. For example, the mode of growth and habitat of a given microbe determine largely how it is communicated to an individual, whether through air, water, food, or bite of an insect, and determine, therefore, to a very large extent the foeus of primary growth in the body. It is the aërobic or anaërobic properties of the microbe that determine largely where and how it grows within the organism. Whether it produces endotoxins or ectotoxins has a material influence upon the course of the infection caused, and the reaction of the body to its growth within the tissues. These and allied matters constitute what we may term the special pathology of the infec-

tions. To enter into these matters fully might well take up several volumes. The most that we can undertake in the following few pages is to note the outstanding features in connection with the more important infections, impressing upon the reader the main facts so far elicited as regards the specific microbes; their properties as these bear upon the production of disease; their mode of entry into, and growth within tissues, the naked eye and minute anatomy of the specific lesions which they induce. This is neither a text-book of bacteriology nor a work upon clinical medicine. Thus no attempt will be made to present a detailed description of the morphology and cultural characteristics of the different microbes; nor again to give a full picture of the course of each disease: only those points will be dwelt upon which serve to impress upon the reader the relationship between the causative agents and their effects.

It is not a little difficult to determine the order in which to deal with these various infections. The most rational classification appears to us to be the following:

    I. Diseases associated with the lower bacteria.
        (*a*) Micrococci; (*b*) bacilli and spirilla.
   II. Diseases associated with higher bacteria.
        (*a*) Spore-bearing; (*b*) branching or potentially branching
           forms.
  III. Diseases which are associated with filterable viruses.
  IV. Diseases which are associated with higher plant forms—moulds.
   V. The spirochetoses.
  VI. Diseases associated with protozoal forms.
        (*a*) Amœbæ; (*b*) Sporozoa; (*c*) Flagellata.

DISEASES DUE TO LOWER BACTERIA

Infections due to micrococci may be classified into four main groups: (1) those due to the pyococci; (2) those due to streptococci; (3) Mediterranean (or Malta) fever; (4) those due to the Gram-negative diplococci.

Pyococcal Infections.—Under this heading we bring together conditions set up by a closely related group of Gram-negative cocci, forms indistinguishable under the microscope, possessing like biocultural characters, differing in little save appearance and coloration of the growths upon solid media, and in virulence. The type member of the group is the *Aurococcus,* or to give it the indefensibly cumbrous name with which Rosenbach christened it, the *Staphylococcus pyogenes aureus.* In actively suppurative conditions this form is often to be isolated in pure culture, but in like conditions, which as yet we have not learned to distinguish clinically, we may encounter other members of the group— the S. p. albus, S. p. citreus, M. cereus flavus, etc. At the most this may be said, that the more acute the suppurative process, the more likely are we to isolate the aurococcus, with its golden-yellow pigment-production upon solid media.

This group of microbes is widely distributed in nature, and adapts itself easily to growth either at the ordinary atmospheric temperature or at that of the body of warm-blooded animals. Thus it is that cul- tures of the various members can be obtained from the surface of the healthy skin, the mouth and pharynx, and the intestines. These cocci are aërobes and facultative anaërobes; entry into the body is most commonly through the skin, next most commonly through the pharynx (and tonsils) and the intestinal tract.

Fig. 47

Aurococcus. Agar culture. × 1000. (After Migula.)

How abundant are members of this group as saprophytes upon the skin has been demonstrated in the many studies upon sterilization of the hands. It is found impossible to obtain complete sterilization of the skin. Very shortly after treatment calculated to destroy all bacteria there present, swabs made from the surface afford in nearly every case bacterial cultures, of what Welch has called the *M. epidermidis albus.* Clearly the organism has been growing deep down in the ducts of the sudoriparous or sebaceous glands and is brought to the surface in the secretions. From its growth characters, it is evidently an attenuated or non-virulent pyococcus albus. To it is due the development of "stitch abscesses" along the course of cutaneous ligatures. The effect of the ligature is to cut off the capillary nutrition of the tissue included within the ligature, to depress its vitality and resisting powers, and so favor the multiplication of the cocci from the deeper part of the skin along the catgut or silk into the tissues beneath. Growing, the cocci gain in virulence, become abundant, and their endotoxins, as some of them are destroyed by leucocytes attracted to the damaged area, attract other leucocytes in such numbers that a true abscess is produced.

As Ogston first pointed out, it is members of this group, and particu- larly the Aurococcus, which most often are found in boils (furuncles) either in pure culture or associated with Streptococci. The boil is a subcutaneous abscess. As already indicated, the products of these pyococci, notably the endotoxins, are strongly chemiotactic for the

polynuclear leucocytes. Take a small glass tube open at one end, an inch or so in length; place in this a drop or two of an old macerated broth culture of a pyococcus, fill with physiological salt solution, and insert into the jugular vein of a fair-sized animal: in the course of a few minutes the mouth of the tube will be packed with leucocytes which have wandered out from the blood stream.

Here, to prevent repetition, it will be well to state the present views regarding the mode of action of pathogenic bacteria (and they are the majority) which produce endotoxins: these views are based upon, and well exemplified by, the studies on the experimental production of pyococcus infection. If by a fine hypodermic needle a minute amount of an Aurococcus culture be introduced into the subcutaneous or other tissue, and the animal be killed within the next twelve to twenty hours, and the region of infection be studied under the microscope, what is most striking, in a susceptible animal, is the singularly slight evidence of local reaction. It is noticeable that the cocci are evidently proliferating with very little hindrance, and are spreading outward along the surrounding lymph spaces. *The growing cocci as such cause very little irritation.* Only a few hours later do we see an active attraction of leucocytes. What brings about this initial attraction and subsequent phagocytosis of some of the cocci may be either (1) the disturbed metabolism and excreted products of the tissue cells of the part, the nutrition of those cells having been damaged by the mechanical presence of the bacteria filling up the lymph spaces, or (2) the breaking down and liberation of the split products of certain of the cocci, their death being brought about not so much by the action of the tissues as by the very accumulation of the multiplying bacteria preventing due nutrition. Whatever the cause, once leucocytes are attracted to the area they ingest sundry of the cocci, and then digesting them, split up their proteins, thus liberating their soluble and diffusible endotoxins. These, diffusing, cause dilatation of the surrounding capillaries, and migration from them of more and more leucocytes, with more and more phagocytosis. Many of the polynuclears in the centre of the area are destroyed by the strength and concentration of the endotoxins. The endotoxins diffusing out gain entrance into the lymph and blood and set up disturbances at a distance, with febrile symptoms.

At first the cocci were attacked by non-specific lysins, the common proteolytic enzymes of the leucocytes which had engulfed them, and to these non-specific enzymes (lysins of the first order) is due the liberation of the highly toxic endotoxins. Later—if we may reason from analogy and employ the results obtained in studies upon the parenteral digestion of foreign proteins—the leucocytes and other body cells which have absorbed the poisonous split proteins develop specific enzymes (lysins of the second order), which break these down into harmless substances. It is with the production of these specific lysins in excess that the body overcomes the bacteria, that the febrile process comes to an end, and healing ensues.

At times the reaction is not developed until after the cocci proliferating have been carried into the blood stream. In this they may be arrested in various capillary areas, and where arrested may grow and induce **metastatic abscesses.** This bacteriemia, with secondary abscesses in sundry organs and tissues, constitutes the condition of **pyemia.** One particular form of this shows itself by the development of endocarditis.

In other cases, without there being general pyemia, the cocci become localized and grow only in one "tissue of election," and·then often without the primary focus of growth being recognized, the so-called *cryptogenic infection.* A frequent example of such cryptogenic infection is seen in the suppurative *periostitis* and *osteomyelitis* of young children. in which most frequently we gain pure cultures of the Aurococcus.

Streptococcal (including Pneumococcal) Infection.—Two potentially pathogenic forms stand out prominently as accompanying man from the cradle to the grave, and what is more aiding his descent· to the latter place—the one streptococcal and the other bacillary (B. coli). Of the two the streptococcal is the more potent, capable of setting up an extraordinary variety of disturbances.

Around the streptococcus from the very beginning of· scientific bacteriology—the early eighties—has raged one of the gravest of battles: grave not merely from a biological standpoint, but also because of its influence upon our conceptions of disease—the battle of specificity. Ogston's recognition of the chain coccus—the streptococcus pyogenes— as one cause of boils was rapidly followed by Fehleisen's discovery of the streptococcus of erysipelas. Were these two distinct species? Was erysipelas a disease apart, which by contagion caused the development of erysipelas in other individuals? Within a very few years it was proved that both culturally and experimentally the two forms are identical. But in the late eighties attention was called to forms of streptococci which in fluid media developed into long chains (S. longior), and others which gave rise only to short chains (S. brevior), and some held that these possessed a different pathogenicity, and so represented distinct species; and of late years English workers in particular—Gordon, Houston, Poynton and Paine—have by fermentation and other tests sought to establish a long series of species of streptococci. Thus relying upon constancy to reaction to fermentation tests, Gordon among 300 cultures of streptococci isolated from the saliva 48 distinct types.

One member of this group, the Pneumococcus, has for a generation been regarded as a distinct species, even although in the eighties Klein called attention to an epidemic form of pneumonia in which the cocci both in the sputum and cultures were present in the form of chains, and although of late years there has been abundant discussion regarding forms possessing properties intermediate between the S. pyogenes and the Pneumococcus.

The long-continued and very thorough studies of Rosenow, of Chicago, appear to afford the solution of the problem. According to him there

is one species of streptococcus pathogenic in man, but this is capable of great variation according to environment. He brings forward evidence that by passage through the rabbit, and by growth outside the body, it is possible to transmute one strain of streptococcus into the other, to obtain from one single strain, such as the S. viridans, a series of strains which in cultural characteristics and pathogenicity are indistinguishable from the M. rheumaticus, S. pyogenes, the Pneumococcus, and yet other intermediate forms.[1]

Fig. 48

Transmutations of strain of streptococcus according to Dr. E. C. Rosenow. The same magnification (1000) is employed for all. 1, strain "595" as a hemolytic streptococcus, isolated from a case of scarlet fever, from a twenty-four hour culture in ascites-dextrose broth; 2, the same growing as a *S. viridans;* 3, the same after taking on through passage the characters of a pneumococcus; the increased size is due to staining of the capsule; 4, a strain of streptococcus isolated from a case of acute rheumatism in man, slightly hemolytic and producing myositis in rabbits; from a blood-agar slant; 5, a highly virulent pneumococcus received from Dr. R. Cole (from condensation water of blood-agar slant); 6, the same transposed into a hemolytic streptococcus, from condensation water of blood-agar slant; also capsule stain.

Like the pyococci, though not nearly to the same extent, streptococci are to be found saprophytic upon the skin. Their chief habitat is the mouth and pharynx, notably the tonsils. Taking cultures of saliva from 25 normal individuals, Gordon found streptococci ("S. brevis") present to the extent of at least 10,000,000 per c.c. in every specimen. These short chained forms from the healthy throat are not pathogenic to mice. Other streptococci may be obtained from throat and tonsils, of all varieties from forms identical with the small rheumaticus variety up to the streptococcus capsulatus and the diplococcus pneumoniæ. As Marmorek and many others have shown, the lower strains can be increased enormously in virulence by growth in blood serum, or other favorable medium, followed by passage through susceptible animals.

[1] S. hominis, var. pneumoniæ, var. pyogenes, var. rheumaticus, etc.

Admitting this as the best "working hypothesis"[1] yet afforded, it has to be accepted that the different varieties or mutations manifest different cultural characteristics, and, grown upon particular media outside the body, retain them with considerable pertinacity, as also that in the organism they set up distinctive lesions. These we must now discuss. Not to confuse the reader unaccustomed to this newer view of the relationships, we shall employ the old termiology.

The *S. pyogenes* proper is a hemolytic microörganism which does not cloud ordinary broth, found in many acute suppurative conditions, and there presenting a liability to extend along the lymph spaces. Thus, for example, whereas a boil due to the Aurococcus is sharply defined, one induced by these streptococci exhibits a surrounding zone of angry tumefaction. Frequently, whether from slight variation in the properties of the cocci, or from the grade of susceptibility of the individual, lymphangitis is the dominant feature, and we have presented not furunculosis, but various grades of erysipelas, cellulo-cutaneous erysipelas, cellulitis with spreading suppuration in the looser tissues, such as those between the muscles of the limbs, and of the neck.

As might be expected, streptococci, often of pyogenic type, play an important part in inflammations of the throat and tonsils. So abundant are they that at first they were considered the causative agents in diphtheria, and some still cling to the idea that they are the active factor in scarlatina. While denying this, we admit that they are responsible for the most serious complications of this disease—the severe necrotic angina, suppurating glands, many of the cases of bronchopneumonia, and probably some cases of true nephritis. In such cases they are found pathogenic for animals, *i. e.*, are definitely virulent: their toxicity may be such as to induce a membranous pharyngitis, even in the absence of diphtheria bacilli. Peritonsillar abscess and cellulitis are apt to be due to streptococci of the pyogenes type. From the throat they may extend to the middle ear, setting up suppurative **otitis media,** and either by this path or through the upper nasal passages they may extend through the dura mater and set up a suppurative and most acute **meningitis.**

Accompanying this tendency to grow along the lymphatics is the liability to gain entrance into the blood stream, setting up bacteriemia (septicemia). This, indeed, is characteristic of all the pathogenic strains of streptococci. There is no organism more frequently encountered in cultures made from the blood at autopsy: as Flexner demonstrated years ago, streptococci are the most common cause of **terminal infections.** In this way we find the pyogenes strain very frequently responsible for the more virulent forms of **endocarditis** with vegetations and ulceration, of "blood poisoning" (**pyemia**) with embolic abscesses in various

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[1] We say "working hypothesis," for Rosenow's observations still have to be confirmed. Holman, for example, has recently brought forward evidence of value to show that Rosenow's "mutations" may be explained by mixed growth of two or more strains, the one showing little growth until transferred to a favorable medium.

organs, of suppurative inflammations of serous surfaces, of **suppurative periostitis** and **suppurative arthritis** and **periarthritis.**

There is another cavity in which streptococci are normally to be encountered in large numbers—the vagina. Usually these are non-pathogenic, but (1) pathogenic forms may be present, or (2) the lower strains may gain in virulence when they enter the uterus directly or by the blood or lymph stream from tears, and infect the lacerated surface of the placental site after childbirth, this particularly when there is retention of the lochia, or (3) highly virulent forms may be transmitted from an infected case to the healthy lying-in woman by the hand of the obstetrician or the nurse. Streptococci thus are by far the commonest organisms found in **puerperal fever.** From the placental site, either through the uterine wall or, more likely, through the tubes the cocci may gain entrance into the peritoneal cavity, setting up acute suppurative inflammation (puerperal peritonitis). Often there is associated bacteriemia. The observations of Duval indicate that in a large number of cases the organisms of puerperal fever are intermediate between the S. pyogenes and the Diplococcus pneumoniæ, possessing the power of fermenting inulin.

Pneumococcus Infection.—According to Rosenow, if a streptococcus of the type of S. viridans obtained from the tonsils be passed through a series of half-grown rabbits, it eventually becomes converted into a capsulated form, and both in the blood and in cultures is indistinguishable from the Diplococcus pneumoniæ; on blood-agar it is non-hemolytic, and it ferments inulin. The number of "intermediates" encountered by those who have attempted to differentiate between the two supposed species has prepared us for this observation. This diplococcus form was isolated and cultivated by Sternberg from the saliva. It may be gained for weeks and months at a time from the healthy throat. It is most often gained from cases of acute lobar pneumonia in man, or from some of the sequels of the same.

But while this is the case, it may occasionally be encountered in pure culture in conditions unassociated with pneumonia, such as otitis media, acute meningitis, vegetative and ulcerative endocarditis, arthritis and peritonitis, and this more particularly, it seems to us, in the young. In the young also it more frequently sets up a lobular pneumonia than a lobar condition. In other words, the air sacs of the lungs are the seat of election, but, just as in tuberculosis, the organism may at times grow actively elsewhere without involving its favorite site.

So also, accompanying lobar pneumonia, there may be extensive involvement of other tissues. It must be emphasized in the first place that *acute lobar pneumonia is always a pleuropneumonia:* some of the abundant diplococci become conveyed from the air sacs and infect the pleural cavity. Thence through the pericardial lymphatics, or it may be through the blood stream, they may set up a suppurative pericarditis, more rarely a peritonitis. As a matter of fact, we are coming to recognize more and more that lobar pneumonia is often the expression of a

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bacteriemia: that during the acute attack cultures of pneumococci are obtainable from the blood. This bacteriemia explains the later onset of diplococcus endocarditis, suppurative arthritis, and, particularly in children, of meningitis, complicating lobar or lobular pneumonia.

Pneumonia—inflammation affecting the lung substance—is not a specific disease. Very many organisms may set up acute inflammation affecting the air sacs—S. pyogenes, B. influenzæ, the Aurococcus, B. typhosus, and the plague and anthrax bacilli, to mention but a few. There is one characteristic form of inflammation—namely, acute lobar pneumonia (see p. 193) in which the whole or a greater part of one or more lobes may be in the same stage of involvement, and from which in 95 per cent. of the cases the diplococcus is to be isolated. Thus about 5 per cent. of cases of acute lobar pneumonia are due to some other organism, such as Friedländer's diplobacillus or one of those already mentioned. The cut surface of the hepatized or solidified lung is moister and more glairy or mucoid in cases associated with this last named bacillus.

Fig. 49

Section from a lung with acute lobar pneumonia in the stage of gray hepatization. All the fibrin here has been disintegrated: *a*, desquamated alveolar cell; *b*, disintegrating leukocyte; *c*, normal leukocyte.

It is noteworthy that inoculated into the lower animals the pneumococcus shows no predilection for the lung: the result is a bacteriemia which in white mice and rabbits is rapidly fatal. Even when inoculated into the trachea little pneumonia results, unless, as pointed out by Meltzer and Auer, suspension of the cocci is introduced in such a way as to fill a bronchus and its branches. By this means inflammation can be produced resembling that seen in lobar pneumonia.

Admitting this, we have to confess that so far we have come across no satisfactory explanation why in the human disease in adults the disease is limited to one or two lobes, and the rest of the lung is not infected; we are equally ignorant of the mode of onset of the infection, and again of the reason for the occurrence of lobular (broncho-) pneumonia in the child, of lobar pneumonia in the adult. So far as our observations go—and this is the generally accepted teaching—the infection begins as an intense congestion of a lobe or portion of the same, accompanied by great pouring out of blood-stained serous fluid into the air sacs. It may be that this begins in a single lobule, and that the infected exudate rapidly flows over and is inhaled into the territories of neighboring bronchi, so that within a few hours the whole of a lobe is infected and inflamed. From the first the blood-stained sputum contains abundant diplococci. As the fluid distends the air sacs it undergoes coagulation, and the affected lobe becomes solidified—stage of *red hepatisation.* As with the other actively pathogenic members of this group, the pneumococci proliferating in the exudate actively attract the polymorph leucocytes, until the fibrinous network in the air sacs becomes packed with these, and at the same time digested by their proteolytic ferments—stage of *gray hepatisation.* This migration of leucocytes continues until, with destruction of some, and liberation of their enzymes, and the increased production of specific enzymes elsewhere in the body and their discharge into the blood, the time is reached when the concentration of the bacteriolytic substances diffusing into the air sacs becomes sufficient to destroy the diplococci. When this point is reached in the typical disease, there occurs *crisis.* Within a few hours the temperature drops to normal. Within a few days the lobe which had been solid and board-like becomes once more resonant and functions in a normal manner. It is very striking how a few hours before the crisis the sputum contains abundant living and virulent diplococci: with the onset of the critical fall of temperature the sputum, while it may reveal abundant diplococci under the microscope, has lost its virulence and affords few cultures.

Further, while simultaneously the diplococci may be setting up a purulent pleurisy, suppuration proper does not occur in the air sacs: or perhaps we should say that in them the polymorph leucocytes are too densely packed to form true pus, and the accumulation being strictly *outside* the tissue, does not, save in old people and those of low vitality, lead to necrosis and digestion of the lung tissue. Where such necrosis and gangrene of the lung complicate lobar pneumonia, it is generally found that there is mixed infection.

And lastly, the resolution and restoration to normal is not accompanied by expectoration of the contents of the air sacs—the cough and expectoration following the crisis are singularly slight: nor again, judging from the blood picture, do the leucocytes migrate back into the blood stream in any large numbers.

The post-critical albumosuria indicates that, as pointed out by

Professor von Müller, the leucocytes undergo self-digestion (autolysis) and dissolving, their products are absorbed, the alveoli becoming once more air-containing. Where resolution is delayed the presence of the exudate in the air sacs is apt to stimulate a process of organization, capillaries pass into the exudate along with fibroblasts, and these small plugs of newly formed fibrous tissue partly fill the air sacs (see Fig. 50).

FIG. 50
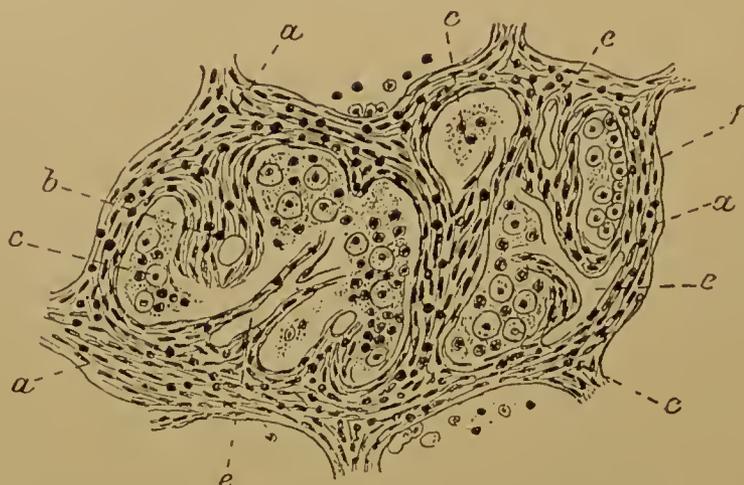
Delayed resolution in a five-weeks' pneumonia. *a*, new-formed connective tissue, developed in the septa; *b*, connective-tissue growth in the alveolus; *c*, remains of exudate; *e*, new bloodvessels; *f*, alveolar epithelium, regenerated. (Kaufmann.)

Streptococcus Capsulatus Infection.—This, while sometimes recorded as affecting the lungs, is more often found in connection with the upper air passages, the frontal sinuses, antra, etc. We deal here with long chains of capsulated streptococci forming large glairy colonies, even on ordinary agar media, very different from the fine pinpoint colonies of the pneumococci. The suppurative conditions set up are in general of a less acute, more prolonged type.

Acute Rheumatism, Streptococcal Endocarditis, Muscular Rheumatism and "Rheumatoid" Affections.—It is wise to consider these together, and that because the evidence is accumulating that they are all caused by closely related strains of streptococci, and because while they may occur independently, they are apt to be associated. Acute rheumatic fever may occur with or without endocarditis, streptococcal endocarditis may or may not be accompanied by arthritis and myositis: myositis may or may not be accompanied by periarthritis and other "rheumatoid" changes.

Acute Rheumatic Fever.—Acute rheumatic fever is characterized by sharp onset with rigors and chills, high fever with hot dry skin, swelling and pain in several joints with resolution by lysis. Like other streptococcal diseases it has a distinct tendency to recur. For a long time regarded as a metabolic disorder, its course is so typically that of an acute infection that bacteriologists have been convinced as to its microbic causation, and in English-speaking countries have been divided into two camps, those supporting Poynton and Paine, and regarding it as

lue to a specific diplo-streptococcus, the *M. rheumaticus*, and those
on the contrary who find non-specific streptococci more nearly allied
to the *S. viridans*, a form which is non-hemolytic, but grown on blood-
agar becomes surrounded by a greenish halo. Both parties have found
that the organisms they have isolated, when inoculated into rabbits
will set up a non-suppurative arthritis with or without endocarditis.

The truth appears to be, that we deal with strains of streptococci
very closely allied, both—or all—of which will induce acute rheumatism,
and that by passage through the rabbit the M. rheumaticus can be con-
verted into the more typical S. viridans
type. The characteristics of the M.
rheumaticus are, that in the affected
joints and synovial membranes it ap-
pears as a minute diplococcus, smaller
than the ordinary streptococcus; that
it will grow actively at temperatures
below that of the body; that it pro-
duces formic acid and is non-hemo-
lytic; grown outside the body it de-
velops into short chains, and upon
milk media produces considerable acid.
It may produce endocarditis of a low
type—verrucose endocarditis. This
Rosenow has shown is of embolic origin.
Rheumatic fever and acute endocar-
ditis are characteristically diseases of
early life. He points out that in early
life the heart valves are vascular, with
fine arterioles which run into the prox-
imal two-thirds of the cusps; as adult
life approaches, and the cusps become
more fibrous, these are obliterated.
Experimental inoculation of half-
grown rabbits with these rheumatic
strains shows that in a large proportion
of the animals treated at the end of
twenty-four hours fine hæmorrhages

FIG. 51

Acute rheumatic fever. Early stage of
"Aschoff's node," with degeneration and
disappearance of heart muscle fibres and
coincident great swelling and disruption of
endothelial cells with (in the main) slight
lymphocytic infiltration. (From a section
prepared by Drs. Thalhimer and Roths-
child.)

are to be seen within the substances of the valves. Microscopic ex-
amination shows that conglomerate chains of streptococci become
arrested in the terminal arterial capillaries. As, from the structure
of the cusps, there can be no active migration of leucocytes, the
cocci grow until they form a complete embolus. The hæmorrhage
is of the same nature as that seen in a red infarct due to the mal-
nutrition of the capillaries beyond the block with back-flow of blood
into them.

Another characteristic lesion of acute rheumatic fever, first fully
studied by Aschoff and Tawara, is the presence in the myocardium of

miliary cell nodes (see Fig. 51). These consist in the main of swollen cells of endothelial type, with some infiltration of lymphocytes. They appear to be due also to embolic blockage of myocardial capillaries with the streptococci, destruction of the streptococci, and at the same time of a few heart muscle fibres in the immediate vicinity, with swelling and proliferation of the capillary, endothelial cells. The end-stage is the development of a small area of fibrosis.

With regard to "rheumatism," it must always be kept in mind that this is a name which from its vagueness ought to be abolished; the name is applied both to pains in the joints and pains in the muscles. These pains in the joints may be caused by more than one microbe, by the gonococcus, for example, when we speak of "gonorrheal rheumatism," more properly **gonorrheal arthritis**; and the term muscular rheumatism is evidently used also for a variety of conditions from the accumulation of the products of metabolism which occurs after unaccustomed exercise, up to a true infective myositis. Only when we speak of "acute rheumatic fever" do we signify a particular order of infections. For long, this, like all other rheumatic states, was regarded as a metabolic disturbance, although for many years bacteriologists have from its character been convinced that it is to be included among the infections. Of late years, observations, especially in England and North America, have accumulated, proving its streptococcal causation. Since Rosenow's convincing investigations, it has become unnecessary to take part in the debate whether the causative agent is a diplo-streptococcus or a streptococcus proper. We may state that strains of streptococci of somewhat different orders induce the condition. It has been noted so often that rheumatic fever is ushered in by tonsillitis, that we are not unprepared for the observation that in this disease organisms are to be obtained from the tonsils indistinguishable from those isolated from the joints and peri-articular tissues. Our conception of the disease, therefore, is that from living a saprophytic existence in the crypts of the tonsils, cocci, whether of the M. rheumaticus or the S. viridans type, gain entrance to the blood stream and are transported to the capillaries of the synovial membrane; in the susceptible individual under suitable conditions, instead of being destroyed they undergo multiplication, set up inflammation and, being carried into the joint cavities, spread to the whole serous surface, inducing thus a condition comparable with a serous pleurisy. Less commonly streptococci of higher virulence enter the joint and cause a true suppurative arthritis—comparable with an empyema.

Simultaneously the M. rheumaticus is apt to become arrested and grow in another area—namely, in the terminal arterioles of the cusps of the heart valves of those below adult age. It is a striking fact that acute rheumatic endocarditis is a disease of youth and does not primarily affect the adult. Parallel with this is the fact that in the young the proximal two-thirds of the heart valves are vascular, the vessel becoming obliterated and disappearing at about the eighteenth years

As Rosenow has demonstrated in half-grown rabbits, following upon the inoculation of the M. rheumaticus into the ear veins, in twenty-four hours a fair proportion of the animals on being killed exhibit small hæmorrhages *within the substance of the cusps.* On section it is seen that these hæmorrhages follow a blockage of the fine arterioles or capillaries by clusters of the cocci. It appears that if the cocci become arrested in more richly vascular areas, there is a rapid migration of leucocytes with destruction of the cocci. Here in the poorly supplied valve tissue

Fig. 52
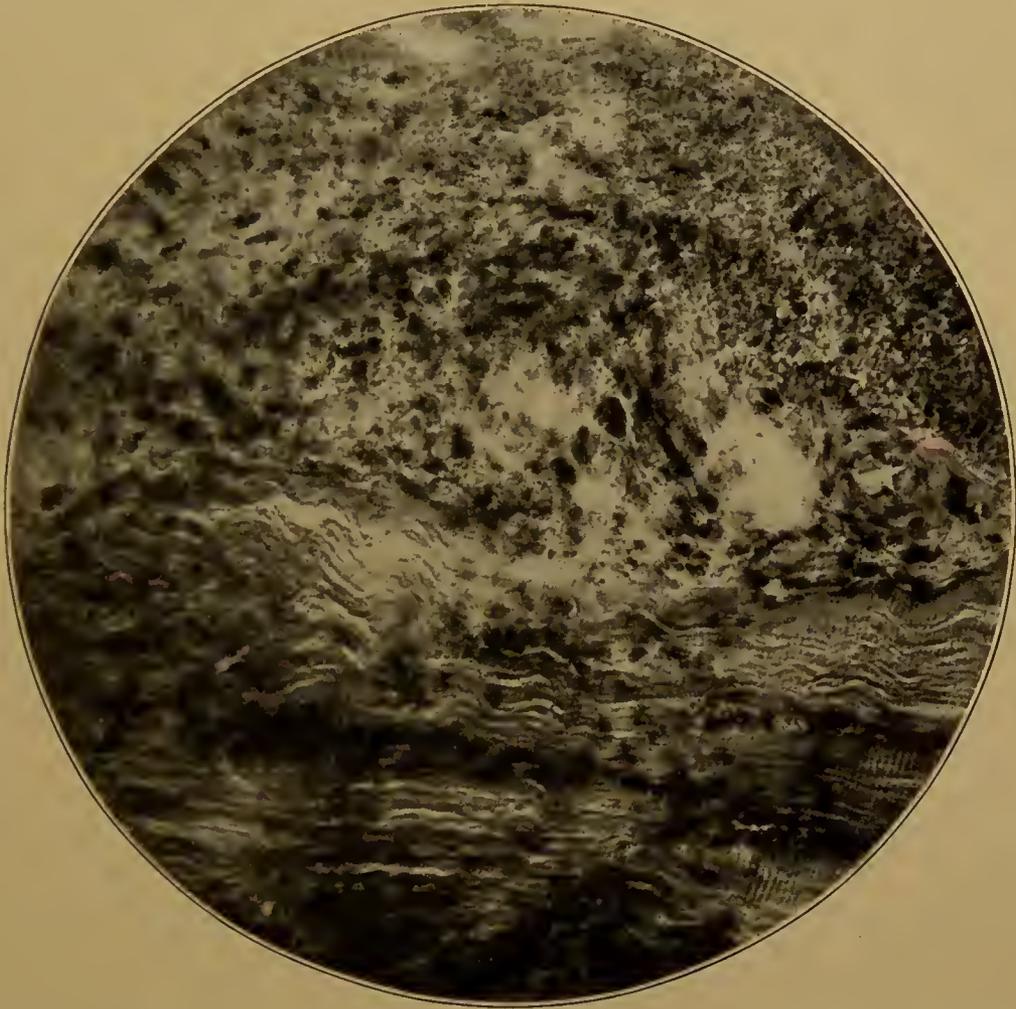
Rheumatic myositis, human. × 230. The muscular tissue is infiltrated with large cells of endothelial type and lymphocytes, and in the upper half of the field is indistinguishable. (Dr. E. C. Rosenow.)

few leucocytes can enter the field: the cocci introduced multiply until they form complete emboli, blocking the vessels. The subsequent hæmorrhage and cell destruction cause a greater attraction of leucocytes, and with this bacterial growth is arrested. Thus the typical rheumatic endocarditis is slight and of the verrucose variety, small nodes occurring in the substance of the valves.

Streptococci of the viridans type, on the contrary, are more liable to be arrested and cause reaction in the mitral and other heart valves

than in the peri-articular capillaries. They are of a somewhat higher
grade of virulence, and growing in the valve substance, may set up so
much necrosis as to cause destruction of the overlying endothelium
covering the cusp. Following upon this, there are deposits of blood
platelets and fibrin over the necrosed and denuded area, and develop-
ment of endocarditis with vegetations. Organisms of this grade are
found responsible for Libman's "subacute endocarditis" with or (more
often) without accompanying arthritis. Libman's S. endocarditis is
identical with Rosenow's culture of the viridans type.

Fig. 53
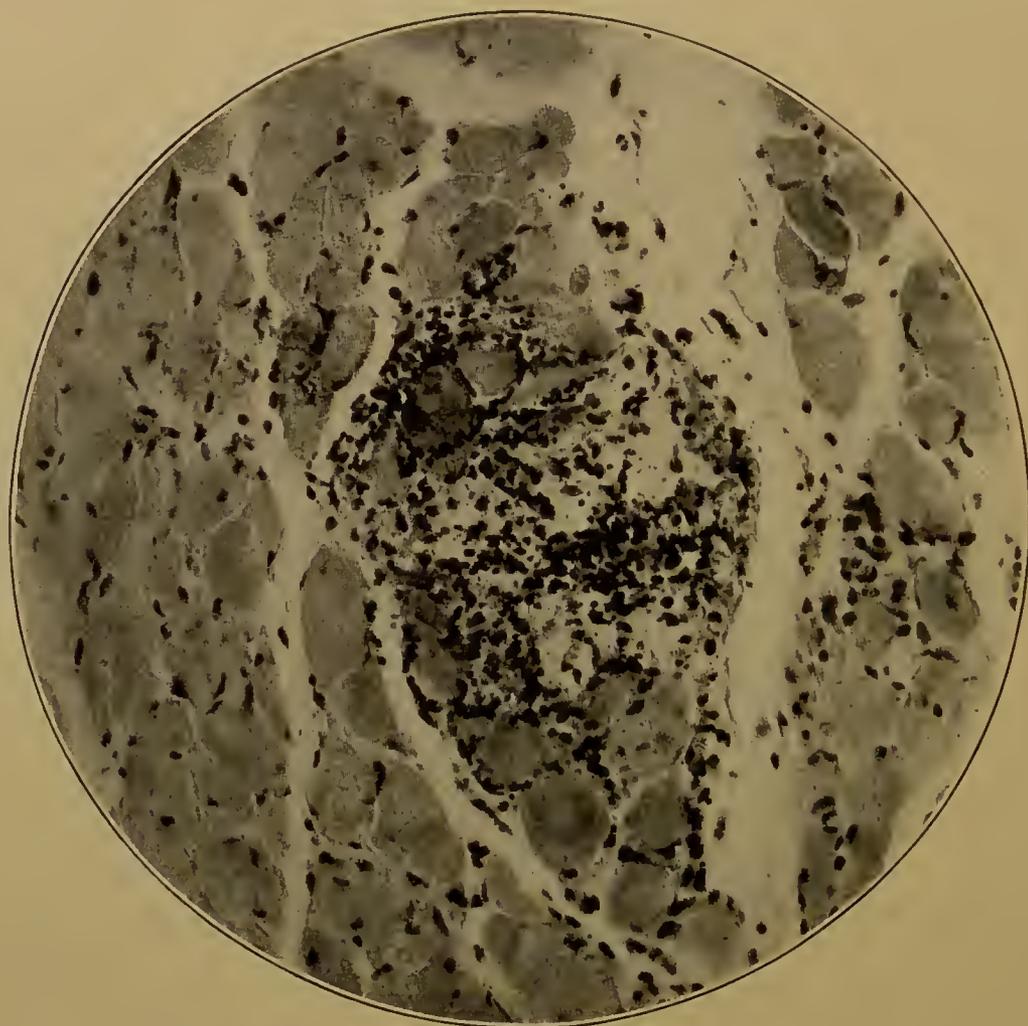
Experimental rheumatic myositis produced in the rabbit by intravenous inoculation of streptococci
of a particular grade of virulence. To compare with the natural lesion in man shown in Fig. 51.
× 230. (Dr. E. C. Rosenow.)

Lastly, by passing the arthritis-producing cocci through a series of
four or more rabbits, Rosenow obtained a stage in which a true muscular
rheumatism was produced, with or without arthritis and endocarditis.
The cocci became arrested in the muscle capillaries, more especially
near the tendinous attachments of the muscles. The process is the same
as that occurring in the other capillary regions: there is temporary
proliferation of the cocci: blockage: ingestion of the cocci by the vascular
endothelium with little attraction of leucocytes: death and lysis of the

cocci: necrosis of the surrounding muscle fibres or cells (Zenker's degeneration). In this way there are produced whitish areas in the muscle visible to the naked eye, from one-eighth of an inch in diameter to patches one-half an inch across where several areas become fused. The degenerate areas may become completely regenerated, or on the other hand may be replaced by connective-tissue proliferation and fibrosis.

In all these cases it is evident (1) that we deal with strains of streptococci of a relatively low order of virulence; (2) that these enter the blood stream from some superficial focus, such as the tonsils, the gums affected with pyorrhœa alveolaris or the lower digestive tract; (3) that in most organs of the body the richness of the circulation is such that arrest is rapidly followed by destruction of the cocci; (4) that according to the strain of the coccus (size of chains, etc.) arrest in particular areas is not followed by rapid destruction, but conditions favor the growth of the cocci until they produce, on disintegration, so much toxic matter as to develop a local necrotic lesion: (5) that the body develops but small quantities of specific immune bodies against streptococci, from which it follows (6) that as these cocci may be saprophytic for long periods in the tonsils and elsewhere upon the surface, so we are apt to meet with recurrent attacks of all these streptococcal infections.

Holding these views, we become convinced that the peri-articular, muscular, and other fibroses characteristic of so-called "chronic rheumatoid" affections, or "rheumatic gout" represent the summation of repeated insults of this nature set up in the main by streptococci of low virulence: that, in short, these affections are the outcome of long-continued subinfections of streptococcal origin.

Mediterranean (Malta) Fever.—This is an endemic, at times epidemic, fever characterized by long duration, frequent relapses, and low mortality, occurring most commonly in countries bordering on the Mediterranean, but recognized also in India, South Africa, the West Indies, and South America.

After prodromal symptoms of languor and dyspepsia, severe headache, drowsiness, enlarged spleen, and rheumatic pains in the limbs usher in the fever proper. There is a moderate fever, with irregular temperature chart, lasting for ten days or so, a return to the normal for about the same period, followed by a relapse. These frequent relapses are, indeed, the striking feature of the disease. As indicating relationship to those diseases caused by the streptococcal group, the rheumatic period may give place to actual arthritis with effusion, and there is a distinct liability to endocarditis.

As first shown by Sir David Bruce, the associated organism is a small, non-liquefying Gram-negative coccus, seen singly or in pairs in the tissues, in short chains in fluid-culture media, taking on a bacillary form when grown for some days on solid media. It has been isolated from the blood, spleen, liver, kidneys, lymph nodes, gall-bladder, and urine (after the fifteenth day) of affected individuals, and has been

gained from the milk of goats and cows in the endemic areas. The indications are that, in general, it is a milk-borne disease, the goat in particular acting as carrier. Stoppage of the use of the offending fresh milk rapidly arrests the appearance of fresh cases.

There are no specific lesions, save the presence of an enlarged congested spleen, with soft friable pulp, without associated lesions of the Peyer patches.

Infections set up by Gram-negative Diplococci.—Of these there are two in particular, epidemic cerebro-spinal meningitis and gonorrhœa. It appears to be well established that certain epidemics of nasal catarrh and inflammation of the accessory nasal sinuses, as again rarely of the conjunctiva, [are]set up by a third member of the group, the M. catarrhalis.

Fig. 54
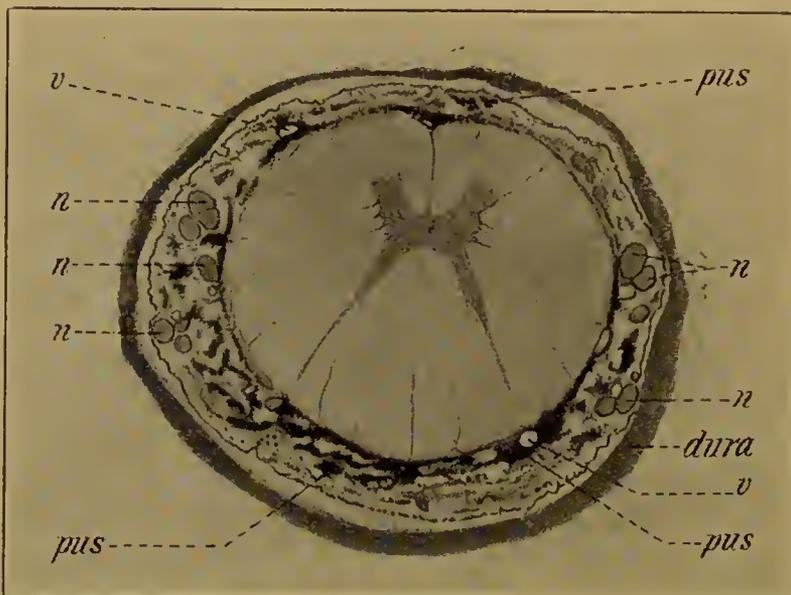
Acute cerebro-spinal meningitis. Section through dorsal cord of child, with intact membranes. Enlarged four times. Dura distended, large pia-arachnoid space. It is seen that the masses of pus cells (which stain darkly) are much more abundant on the dorsal aspect (below). *n, n,* nerve roots cut across transversely and obliquely; *v, v,* dilated veins.

Epidemic Cerebro-spinal Meningitis.—Between gonorrhœa and cerebro-spinal meningitis there are not a few points of resemblance. Both, it is held, begin as infections of exposed mucous surfaces. Swabs and cultures made from the upper nasal passages of individuals affected with this specific meningitis afford the Weichselbaum diplococcus. To this not all individuals are susceptible. Adults in particular are liable to be immune. Many individuals in a household in which there is a case of this form of meningitis may yield the diplococci from their nasal passages. In the susceptible individual we suppose that leucocytes convey the cocci through the cribriform plate into the pia-arachnoid spaces. Multiplying, these become extensively disseminated through all the territory washed by the cerebro-spinal fluid. At first free in the fluid, they are rapidly and actively taken up by the polymorph leucocytes, until in the less acute cases no free cocci are to be seen. By these

they may be digested and dissolved. We have performed the autopsy, and that within four hours after death, upon a little child dying in six hours after the onset of acute symptoms, in which with intense congestion and abundant cerebro-spinal fluid only rare diplococci were to be recognized in the smears, but in the leucocytes abundant paired "ghosts" of the cocci. Here, evidently, the very activity of the lysis and wholesale liberation of the endotoxins was the cause of death.

Fig. 55
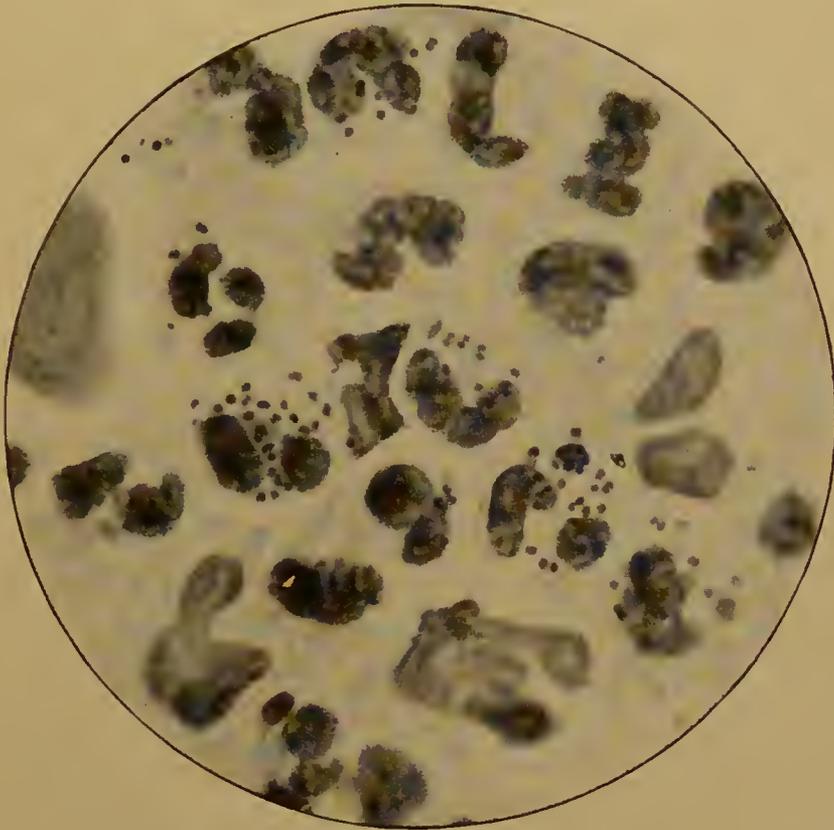
Pus cells from the cerebro-spinal fluid from a case of epidemic cerebro-spinal meningitis, stained to demonstrate the meningococci. (Dr. Hanford McKee.)

The cerebral and spinal symptoms are in part due to the irritant effects of these endotoxins, in part to the compression exerted by the increased amount of cerebro-spinal fluid poured out in consequence of that irritation. Comatose and other diseased states of the nervous system are apt to be greatly relieved by lumbar puncture. The gush of fluid from the needle in typical cases is eloquent of the pressure exerted by the increased amount of fluid.

In uncomplicated cases the cocci are confined to the cerebro-spinal fluid and nasal passages. But blood cultures often afford colonies of the cocci (in 25 per cent. of cases according to Elser) and the Gram-negative diplococci have been found in the sputum (along with pneumococci and streptococci) in cases in which there is a complicating bronchopneumonia, in the pus from complicating conjunctivitis and otitis media, and in pus from joints where there has been a complicating

arthritis, and in the pericardium. In the early stages there is a well-marked polymorph leucocytosis.

The main lesion is in the meninges. In cases dying early these present intense congestion; in cases surviving the fourth or fifth day there is heavy accumulation of leucocytes and fibrin along the sulci. This may be most marked over the hemispheres; more commonly is it pronounced at the base of the brain. Not infrequently the cocci and the infection spread into the ventricles of the brain, so that, in consequence of the results of the ependymal inflammation, healing may be accompanied by the development of hydrocephalus. Similar accumulation of leucocytes forming a thick deposit occurs along the spinal cord, especially on the posterior aspect. The brain tissue itself is also injected and œdematous, with some atrophy and reduction of the Nissl bodies. The inflammation may involve and extend along the cranial nerves with development of peripheral neuritis.

Fig. 56
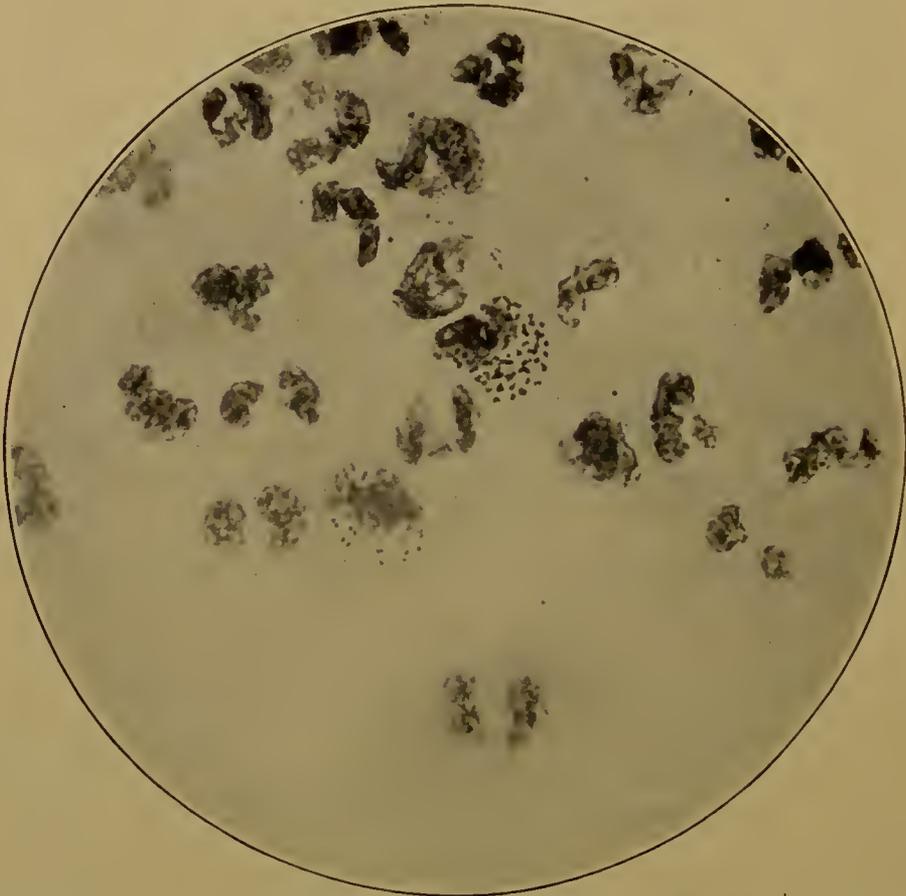
Gonococci in polymorphonuclear cells of pus in the acute discharge. Gram-stain with counter-stain. × 1500. (Dr. Hanford McKee.)

To these changes affecting the cerebral and cerebellar cortex are to be ascribed the rigidity of the neck and opisthotonos. There is still debate as to the cause of Kernig's sign, found so frequently in this and other forms of acute meningitis as to be pathognomonic. It consists in the inability to extend the leg completely when the thigh is at right angles to the trunk.

Gonorrhœa.—Gonorrhœa is a disease confined to the human race; not even the anthropoid apes are susceptible. The seat of election of the gonococcus is the outer genital passage in either sex. Every case in nature is to be traced directly or indirectly to infection by means of the discharge in or from these passages. This does not signify that the gonococcus thrives only in these passages; the contrary is the case.

Fig. 57
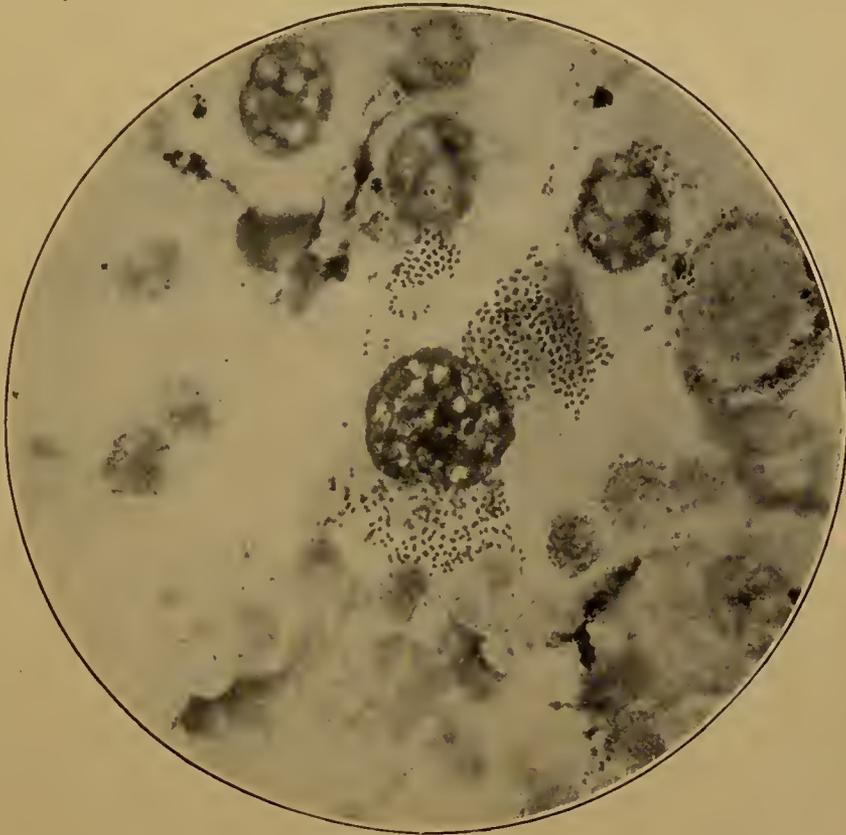
Gonococci in scraped-off epithelial cells of the conjunctiva, from an apparently healed case of gonorrheal ophthalmia; stained by Giemsa stain, to demonstrate the continued growth of the microörganisms within the cells after tolerance has been established. × 1500. (Dr. Hanford McKee.)

The sequence and incidence of events differ somewhat in the two sexes. In the male it is the urethral mucosa that is first involved. The gonoccocci multiplying in the passage are taken up by the cells of the mucosa and set up an acute congestion of the submucosa and discharge of profuse exudate rich in polymorph leucocytes. These actively ingest the diplococei. The picture afforded by a smear from this purulent discharge is scarce to be distinguished from that given by the purulent cerebro-spinal fluid in cerebro-spinal meningitis: both exhibit polymorph leucocytes in abundance, some filled with Gram-negative diplococci; it is to be observed that the bean-shaped units of the gonoeoceus are more equal in size and less irregular. Whether by treatment or by nature the intensity of this local inflammation tends to undergo reduction, until in the course of days or weeks the purulent gives place to a thinner mucoid discharge, in which

eventually no leucocytes and no cocci are to be detected. It must be emphasized that this does not mean that the gonococci have undergone a complete local destruction. It may be laid down that so long as there is a "chronic gleet," even if reduced to a drop of discharge daily, some of the mucous cells removed from the posterior urethra by scraping, as shown by McKee and Campbell, are found to contain intracellular diplococci, and so long as this is the case the individual may convey infection by coitus, and by indiscreet indulgence in alcohol or venery become liable to a relapse.[1] It is this chronic infection of the mucosa that best explains the progressive fibrosis of the underlying submucosa with contraction of the same and production of *stricture*.

This also deserves emphasis, that while in some by the natural vigor of their constitution, or by timely treatment, the manifestations of the disease remain confined to the urethra, in not a few the gonococci spread to other regions. This spread may be either (1) direct, along the genital and urinary passages, or (2) hematogenous. By the first means there may be set up prostatitis, vesiculitis, or epididymitis. While the vesical urine may contain gonococci, the bladder is rarely acutely involved, but occasionally ureteritis, pyelitis, and acute nephritis are set up. More than one observer has gained cultures of gonococci direct from the blood; several cases are now on record of gonococcal endocarditis of the actively vegetative type. Gonorrhœal iritis is not infrequent, and this unassociated with conjunctivitis, so that the origin must be hematogenous. Most frequent of all is the condition of gonorrhœal arthritis affecting particular joints or groups of joints. Along with this is often observed pain in the heel which can scarcely be arthrial, but perhaps is periosteal or from affection of the insertion of the tendo Achillis. A characteristic of this group of maladies is a tendency to recur in spite of treatment.

In the female the primary affection is not so severe. Abundant saprophytic microbes gain lodgement in the vaginal cavity, and many conditions leading to vaginal congestion may be followed by active growth of certain of these, such setting up irritation and a condition of **leucorrhœa**[2] with discharge of thin purulent fluid. Such discharge is most frequently not gonorrhœal at all, although to such a leucorrheal discharge a gonococcal infection may be superadded. Primary gonorrhœa may be overlooked by the individual and regarded merely as a severe and obstinate attack of "the whites." The parts mainly and most often infected are the urethra and vagina. By ascending infection while the uterus is strikingly resistant, the tubes are frequently involved; in fact, the gonococcus is the commonest cause of acute or sub-acute salpingitis and—as the result of subsequent cicatrization and closure of the tubes—of sterility. The outstanding histological feature of gonorrhœal salpingitis, as pointed out by Gurd, is the abundant infil-

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[1] Cases are on record of the development of gonorrheal iritis, and detection of Gram-negative diplococci in the urine, fifteen and even thirty years after primary infection.

[2] λευκός (leukos) white, ῥέω (rhoia) a flow.

tration of the submucosa with plasma cells. It demands note that gonorrhœa acquired at the time of or subsequent to conception has little effect upon the embryo or upon the course of pregnancy: the child does not become infected while *in utero;* indeed, pregnancy by raising the resisting powers of the mother often arrests the gonorrhœal process and renders it latent, to become active again after parturition, more particularly in the tubes. This explains a group of cases in which the wife becomes barren after the birth of the first child. The act of birth, however, exposes the child to the danger of infection of the conjunctiva.

Fig. 58
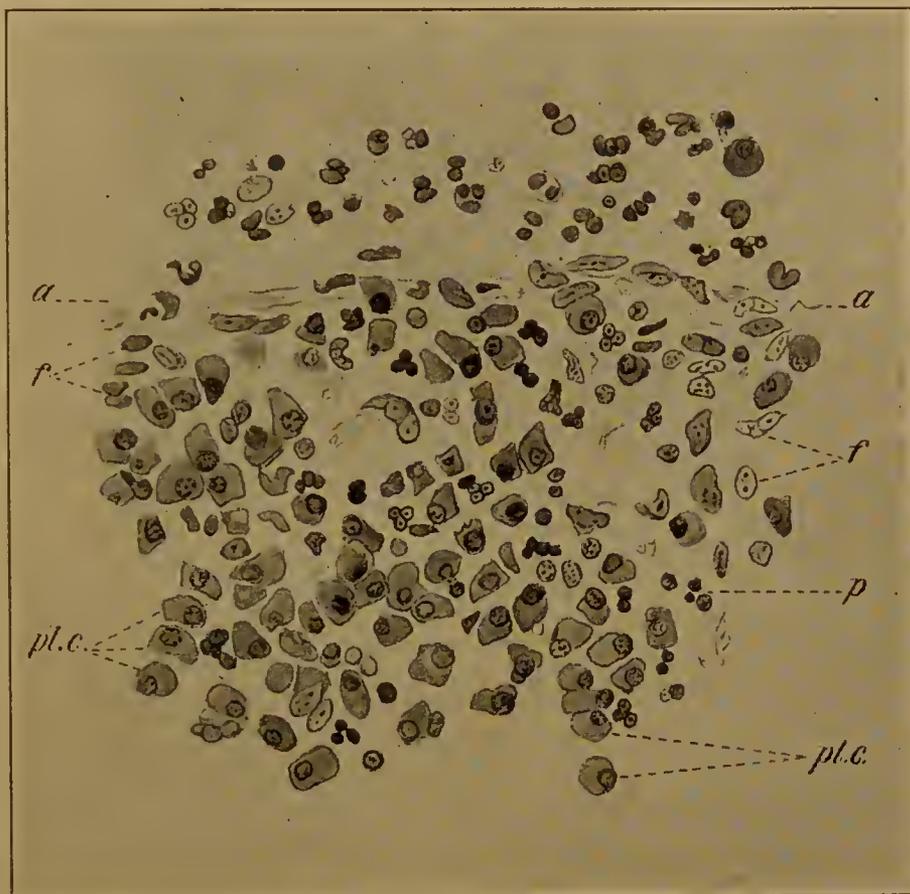
Gonorrhœal salpingitis. The lining columnar epithelium has wholly disappeared; the line from *a* to *a* indicates the separation between the lumen of the tube, above, and the submucosa, below. In the lumen are mainly abundant polymorphonuclear leucocytes. In the submucosa mainly plasma cells.

Owing to the free communication between the tubes and the peritoneal cavity, gonorrhœal salpingitis tends to lead to peritonitis and oöphoritis. In mild cases the peritonitis is localized and pelvic, but it may become generalized. In the female as in the male the gonococci may enter the urinary tract and the blood stream, and induce on the one hand renal disturbances, on the other metastatic inflammation of the endocardium, joints, iris, etc. These, however, are less frequent in the female than in the male; more frequent on account of the relationship of the parts, is infection of the anus and rectum, infection occurring through contamination by the vaginal discharge. It is by a similar process

of contamination, this time through the agency of towels, etc., that epidemics of gonorrhœal vulvovaginitis may assume a wide range in infants' and children's hospitals. So, also, until the last few years, ophthalmia of the newborn was a frequent event, due to gonorrhœal infection of the conjunctiva by the vaginal secretion during the passage of the head into the outer world, and a large proportion of all cases of blindness must be attributed to this condition. By opening the eyelids and instilling a few drops of silver-nitrate solution between them immediately after birth, this grave malady is today easily prevented, gonococci being peculiarly susceptible to the action of silver salts.

DISEASES DUE TO PATHOGENIC BACILLI

What is perhaps the most simple and useful classification of these diseases is into groups caused by:

I. The typhoid-colon group, including B. typhosus, paratyphoid bacilli, B. enteritidis, B. coli, B. dysenteriæ.
II. The mucosus capsulatus group.
III. The hæmorrhagic septicæmia group, e. g., B. pestis.
IV. The B. influenzæ group.
V. The cholera group.
VI. Spore-bearing bacilli.
VII. The diphtheria group.
VIII. The infective granuloma group.

The organisms associated with the first five of these classes are Gram-negative, those of the last three are Gram-positive.

1. **Typhoid-colon Group.**—In the typhoid-colon group we have a series of infections which possess much in common: infections orginating characteristically from the intestines, with the main proliferation of the bacteria in the intestinal wall, but apt to spread thence into the mesenteric lymph nodes and into the blood. In the blood itself there is little or no proliferation, but the bacilli may be carried to and arrested in various organs. The bacilli are agglutinated by relatively high dilutions of the blood serum of affected individuals. That blood serum is liable to agglutinate cultures, living or dead, of other members of the group, but this in distinctly lower dilution. The different bacilli, like the diseases which they orginate, have much in common. Morphologically they are not surely to be distinguished.| All are Gramnegative, non-spore-bearing, tending to vary considerably in length, while constant in breadth. They vary in the number of (peritrichous) flagella possessed, but flagella and motility cannot be regarded as specific; thus ordinarily, the typhoid bacilli are very actively motile with numerous flagella, but non-flagellate, non-motile strains have been recorded.

Typhoid (or Enteric) Fever.—Clinically this is a typical "fever." As such, it is characterized by an incubation period of about fourteen days, ending with prodromal symptoms of lassitude, headache,

backache, etc., which in their turn usher in the "onset of fever," as shown by rising temperature and increasing sensation of illness. This is succeeded by a daily rise of temperature during the next few days until the fastigium is reached, during which there is a daily variation similar to the normal; but it may be at a level four degrees or so higher, ending after a week or so with the supervention of a temperature still high, but more regular, which after a few days gives place to a daily fall, a stage of lysis ending in the resumption of normal temperature, and convalescence. Beyond recalling these main phases, it is not for us to enter deeply into the clinical features. Our duty is to describe the pathological findings, correlating them with what is known concerning the bacteriology of the disease.

FIG. 59
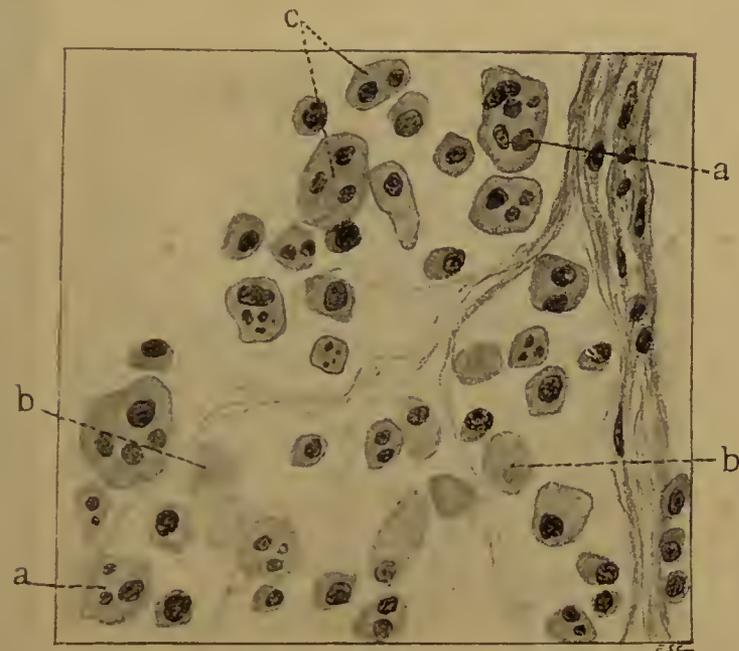
FIG. 60

From a typhoid lymph node to show the swollen endothelial cells or macrophages (*a, a*) acting as phagocytes; *c*, different stages in development of same; *b*, the same undergoing disintegration.
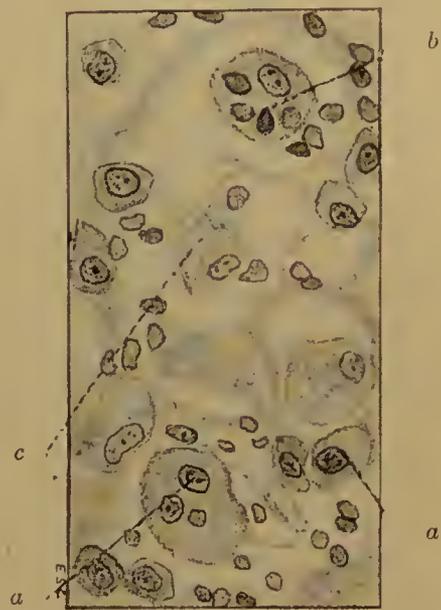
Splenic sinuses from a case of typhoid fever, to show phagocytosis by swollen endothelial sinus cells (*a, a*). These contain red-blood corpuscles, in various grades of decoloration and disintegration; *b*, a smaller endothelial cell; *c*, sinus cell undergoing disintegration.

For us, therefore, the incubation period is that in which the typhoid bacilli which have gained entrance into the alimentary canal, and have mutiplied in the lower part of the ileum, become further transported by leucocytes through the mucosa into the Peyer's patches, and it may be also into the solitary lymph follicles of the submucosa. The bacilli afford practically no ectotoxins. As a result at first they multiply without hindrance and without causing any serious reaction. By analogy with what happens when we introduce the bacilli into the peritoneal cavity, we imagine that while they do not actively attract leucocytes, some of the bacilli are taken up by the endothelial cells of the lymph

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channels and by such polynuclear cells as happen to be in their neigh-
borhood in the lymph nodes, and become digested with liberation of
their endotoxins, and these may set up a local irritation or stimulation
of the more abundant lymphocytes and of the endothelial cells. But
not until these cells are actively stimulated in this manner to destroy
the bacilli are the endotoxins liberated in sufficient quantities to diffuse
into the blood stream, and, acting upon the nerve and other cells at
a distance, to set up first the prodromal malaise and aches, and later,
as the destruction becomes more extensive, to induce the febrile temper-
ature reaction.

Before the local reaction is at its height, as early as the third
day or even the first day of the fever, blood cultures reveal that
the bacilli gain entrance into the blood stream. There is no evidence
that they multiply in the circulating blood, but if arrested in certain
capillary areas there is evidence that they may continue to multiply.
In this way we explain many of the lesions to be presently noted.

We owe to Mallory the fullest study of the histological changes in
typhoid fever, and his description will be substantially followed. Quite
the most striking feature in the Peyer's patches—and the same is true
in the affected mesenteric lymph nodes of the ileocæcal angle—is a
notable increase in the number and size of the cells of endothelial type—
cells with abundant cytoplasm, and oval, pale nuclei. Cells of this
order fill the peripheral lymph sinuses; they are to be found also in the
surrounding lymph sinuses of the villi and mucosa. From the swollen
condition of the lymph-vascular endothelium and the presence of mi-
toses in the same, it must be concluded that they are of lymphatic
endothelial origin. But similar cells are present in the centres of the
nodes, and here evidently originate from the lymphatic reticulum.
With proliferation of these cells the Peyer's patch increases greatly in
size. Progressively they replace more and more the lymphocytes,
until these may be present as little more than a fringe toward the
periphery of the individual nodes. *Polynuclear leucocytes are strikingly
few and far between.* The endothelial leucocytes are actively phago-
cytic and take up lymphocytes and erythrocytes in abundance. With
this, however, they are peculiarly liable to undergo necrosis and die
in situ; in so doing they become centres for fibrin production, first within
their own bodies, and later by extension through the immediately sur-
rounding tissue. Whether through participation of the endothelium
of the veins in this production of endothelioid leucocytes and then
breaking down, or by extension of the fibrin formation through their
walls from the perivascular lymph space, individual veins and venous
capillaries become thrombosed, with, as a result, necrosis of the area
drained. Beginning with scattered areas of vascular obstruction, the
Peyer's patch at first presents scattered small foci of necrosis, involving
not only the lymph node but the overlying mucosa. Gradually the
process extends until the greater part of the Peyer's patch, if not the
whole, becomes necrotic and sloughs out. In the mesenteric lymph
nodes there is the same proliferation, but the necrosis is not liable to

Typhoid fever. Peyer's patches and solitary follicles from a youth, aged twenty years, to show the successive stages. (P M. 31–0S Royal Victoria Hospital.) 1. Abnormally long Peyer's patch (16 cm.) showing congestion and slight swelling, in commencement of ileum, 250 cm. from valve. 2. Patch of normal size, situated a little lower down, 225 cm. from ileocecal valve, showing *état criblée* and at *a*, small area of hemorrhage; at *b*, another hemorrhagic area, with central pale-staining area of necrosis. 3. Patch, 210 cm. from valve. Here the solitary follicles also show swelling; at *c*, hemorrhagic areas with necrotic centres; at *d*, a loosened slough or necrotic area, bile stained. 4. Peyer's patch, some 50 cm. lower down, with two sloughing areas, that at *e* loose and almost detached; at *f*, solitary follicles, with necrotic centres. 5. A patch midway between the last and the ileocecal valve; *g*, hemorrhagic area; *h*, slough becoming loosened; *i*, ulcerated areas, from which the sloughs have escaped. 6 Large Peyer's patch, a few cm. above the valve, showing the completed ulcer. The whole patch has sloughed away, exposing the circular muscular coat of the bowel; *m* solitary follicle that has ulcerated. There were ulcers also in the appendix, cecum, and ascending colon.

be so widespread, and only rarely with softening of the necrotic matter (and possibly secondary infection) does rupture occur with subsequent acute peritonitis.

The necrotic process in the Peyer's patches shows itself from the tenth day of the fever onward. The sloughing accounts for (1) *hæmorrhage* from some vessel involved in the process, and (2) *perforation* of the thinned wall of the gut left exposed. That wall is formed merely of the exposed circular muscle layer of the ileum, the inconsiderable longitudinal muscle layer and the serous coat, and these may be gradually eroded.

If the patient does not die from acute poisoning (typhoid toxæmia), hæmorrhage, or perforation, the ulcer tends to heal. The raised mucosal margins of the ulcer become applied to the base, the mucosal cells proliferate and form a smooth, glistening coat, covering over the exposed muscle layer. If death occurs from other cause a year or so after the attack, it is difficult to recognize the site of the ulcers, save that the lymph follicles have not regenerated.

Thus the successive stages of the typhoidal lesions of the ileum are:

    I.   Tumefaction and enlargement of the Peyer's patches.
    II.   Necrosis.
    III. Localized sloughing with or without hæmorrhage.
    IV. Complete ulceration with or without perforation.
    V.   Healing.

The same process may occur in the solitary follicles of the ileum, and, not infrequently, of the cæcum and colon.

Among the more striking physical signs of typhoid is the marked enlargement of the spleen. This becomes two or three times the usual size and weight—with tense capsule, and pulpy semidiffluent state on section. The condition is not brought about by any enlargement of the lymphoid elements (the Malpighian bodies). These most often show little change. The swelling is due to distension of the sinuses with blood, but even more with endothelioid cells, recalling those seen in the lymph nodes, but here clearly derived, in the main, from the endothelium lining the sinuses. The lining endothelium in itself presents greatly swollen cells, with mitoses. These are seen to be actively phagocytic, taking up erythrocytes and cell debris. Similar cells are seen in large numbers free in the blood which fills the sinuses. These cells present the same tendency, before noted, to degeneration and necrosis, and presumably this necrosis with liberation of thrombokinase explains the conglutination and fusion of clumps of red corpuscles. At times these are seen bound together in a meshwork of fibrin.

There is marked cloudy swelling of the liver, kidneys, and heart muscle. The cloudy change may also involve the skeletal muscles. In the liver in addition to the cloudy change, a marked feature is the presence of **focal necroses**—pinhead areas of death of the liver cells brought about either by this process of swelling of the lining endothelium, or very probably by blockage by large endothelioid cells derived

from the spleen or other regions of the portal system. Cells so swollen and degenerated easily break down and become the origin of fibrin, so that it is difficult in most cases to determine what is the exact origin of these areas of capillary thrombosis and focal death of the liver cells.

In the muscles and notably in the recti abdominis we may encounter small, pale, glistening areas of so-called Zenker's degeneration. Individual fibres or small clusters of fibres take on a hyaline homogeneous appearance with loss of nuclear staining; they are in fact dead. The process is to be compared with the streptococcal myositis already described (p. 200).

The gall-bladder frequently shows a mild grade, more rarely an acute state, of cholecystitis, with abundant catarrhal mucoid discharge. This is associated with the practically constant presence of typhoid bacilli. Sometimes the condition leads ultimately to gall-stone formation (see p. 285).

The characteristic "rose spots" over the abdomen and elsewhere, if frozen by ethyl chloride and so removed with the vessels contracted and bloodless, afford cultures of typhoid bacilli. Evidently these are the result of arrest of the bacilli in the cutaneous arterioles or capillaries, productive of bacterial emboli and subsequent congestion, or more rarely localized hæmorrhage.

Paratyphoid Infections.—Occasionally we encounter, sometimes in an epidemic form, febrile attacks of a typhoidal nature but less acute, beginning, it is true, like typhoid fever, but resolving by relatively rapid lysis at the end of ten days or less. The blood serum in these cases does not agglutinate typhoid bacilli in high dilutions, although it may in lower dilutions. It agglutinates well one or other allied forms of paratyphoid bacillus which may be isolated from the blood or (at autopsy) various organs, *e. g.*, spleen, gall-bladder, etc. At autopsy, while the small intestine may be found congested, and the Peyer's patches swollen, there is an absence of the ulcerative lesions of the ileum.

A more acute enteritis with an incubation period of but a day or two, with violent diarrhœa and at times fatal collapse is seen in some cases of meat poisoning, due to the bacillus enteritidis of Gärtner. This likewise has no specific lesions.

Bacillus Coli Infections.—There is still considerable debate regarding the frequency with which B. coli sets up infection. That it is an extremely common and abundant finding in cases more particularly of generalized and localized abdominal inflammation is universally admitted, but from its very abundance in the normal bowel, and its constant presence there, many are inclined to doubt its power of setting up primary disturbances, and would invoke some other organism, some supposititious anaërobe, for example, as setting up the lesions in the first place, and would like to regard the B. coli as gaining entrance and growth only when the tissues have become thus damaged. Without definite proof, for example, they oppose the view that the B. coli is the

commonest agent in acute appendicits. For our part we see no reason why we should not regard the colon bacilli of the bowel as having the same variable pathogenicity and the same liability to induce disease as we grant to the streptococci of the mouth and throat.

Everyone in hospital practice will recall many cases which enter the hospital under a suspicion of typhoid fever; the disturbance is obviously concerned with the alimentary tract; the patient recovers quickly, gives no specific reactions of typhoid fever, and the disease is called febricula. May not such be the result of B. coli with temporarily increased virulence?

If we grant this, then we find that the B. coli sets up a series of disturbances only a degree less varied and less abundant than that set up by streptococci—and what is more, are prepared to find that it has a like striking liability to undergo transmutation, the variants like those of the streptococci, possessing distinct pathogenic effects. This, at least, in the light of present knowledge, is the simplest explanation of the importance of the large B. coli group of bacilli.

But taking only those forms which at present we regard as B. coli proper, there is this to be said regarding their relationship to infectious diseases: they vary considerably in virulence, and their virulence is liable to be raised in the obstructed bowel. Even after but a few hours of obstruction they may be found in the peritoneal cavity, in the blood, or in the urine and urinary bladder, and this without any obvious focus of growth in the tissues. Rarely the growth in the blood is extreme, with rapid destruction of the erythrocytes, setting up the condition of **microbic cyanosis**. One of us (J. G. A.) has suggested that **hemochromatosis** with deposits of iron-containing pigment occurring first in the coats of the small intestine, is a milder, more chronic condition of like origin and nature.

If the bacillus in large numbers gains entrance into the peritoneal cavity, it is liable to set up an acute fibrinopurulent inflammation, which, where the virulence is moderate or the reaction good, tends to be plastic and self-limited through the fibrinous adhesions; where the virulence is greater it may become rapidly generalized and fatal. As indicated by the varying course of a non-perforative appendicitis, it is impossible to lay down any average duration for a B. coli infection; it may reach its acme in the course of a few hours; it may develop and continue over days and weeks; it may remain strictly localized; it may, on the other hand, extend along the vessels setting up a purulent phlebitis, and in the case of abdominal infections may in this way terminate by loosening and conveyance of the purulent material from branches of the mesenteric into branches of the portal vein, thus setting up abundant embolic abscesses in the liver.

Acute B. coli infections along the course of the systemic circulation, while they may occur, are rarer. Acute meningitis and suppurative otitis media of this nature have been described. Perhaps the commonest lesion of this order is the presence of inflammatory lesions of hema-

togenous orgin in the kidney, frequently as multiple miliary abscesses or as pyelitis. Their occurrence supports the view that a considerable proportion of the cases of B. coli bacilluria, whether in children (in whom this condition is being increasingly recognized) or in adults, is of hematogenous and renal origin.

While admitting the possibility that double or mixed infections may be much more frequent than we are usually inclined to consider, nevertheless from the frequency with which coli forms, and these alone, are to be isolated from peri-appendical abscesses, and from the blood in appendicitis cases, we are inclined to believe that the B. coli is the commonest bacterial factor in the production of what is the most important, as it is the most frequent, local acute infection of the intestinal tract. The usual teaching with regard to appendicitis is that there is a primary catarrhal or other destruction of the mucosa of the organ, leading to entrance of bacteria into the deeper layers. What impresses us as the outstanding histological feature of the inflamed appendix of all grades is the great enlargement of the abundant solitary follicles. We are led to conclude that ordinarily the process of events bears a close analogy to that seen in typhoid fever—namely, a primary carriage of bacteria into the solitary follicles, followed by active proliferation of the lymphocytic elements, and swelling of the follicles. We regard the destruction of the columnar epithelium as due to loss of blood supply, together with compression of the columnar cells between the greatly enlarged follicles, not losing sight, at the same time, of the effect of poor drainage in an organ whose minute lumen may readily become blocked by tumefaction of the mucosa. Deeper necrosis and gangrene may supervene later.

Apart from these acutely suppurative conditions due to the action of virulent strains of the B. coli, or, as in perforative peritonitis, due to the entrance into a serous cavity of overwhelming numbers of bacilli of lower virulence, one of the writers of this book (J. G. A.) has taught for many years that the ordinary B. coli of the intestinal tract is responsible for the production of an important series of more chronic morbid states, which he regards as due to **subinfection** (p. 144). As already pointed out, the recent studies upon rheumatoid conditions have upheld his views as regards the streptococcus. Experimentally by repeated inoculations of doses of relatively non-virulent colon bacilli, well-marked anæmia can be induced. The anæmia of chronic constipation is thus explicable by the entrance and destruction of increased numbers of bacilli of the colon type from the intestine. He has brought forward evidence in favor of the view that pernicious anæmia may be an extreme condition of this nature. Cobbett and the members of the British Commission upon Grouse Disease have demonstrated that the affected animals are at times carriers of such immense numbers of minute nematode parasites in the intestinal cæca that these are completely blocked. According to the number of the worms so did the liver and other organs afford occasional or abundant cultures of B. coli.

They concluded that the parasites caused irritation with minute puncti-form ulcers of the mucosa, favoring the entry of the bacilli into the tissues and circulation, so that the progressive emaciation and death of the birds were due to the intoxication thereby set up.

Years ago the same writer (A.) explained the development of portal cirrhosis of the liver as due to a B. coli subinfection, pointing out that alcohol alone will not induce this condition, but that alcohol and other digestive irritants by setting up intestinal congestion favor this increased passage of leucocytes into the intestinal canal, and through their agency increased entry of intestinal bacteria into the portal blood stream. Only exceptionally will B. coli alone induce hepatic cirrhosis. Opie has solved the problem by showing that chloroform alone (which sets up extensive necrosis of the hepatic cells) will not induce cirrhotic change in the liver, that inoculation of B. coli alone has no effect, but chloroform followed by sublethal doses of B. coli produces an extreme grade of cirrhosis, not to be distinguished from advanced cirrhosis in man. The indications are that alcohol acts as an irritant of the intes-tinal mucosa, and absorbed, lowers the activity or vitality of the liver cells so that now colon bacilli taken up from the portal blood by the endothelium of the hepatic capillaries and Kupffer cells, when disin-tegrated by these cells, liberate toxins of sufficient strength on the one hand to destroy the damaged liver cells, on the other to stimulate the connective tissue cells to increased growth. There is, we may add, in Opie's experiments no evidence of active multiplication of the colon bacilli in the liver nor any suppurative stage or production of abscesses.

Bacillary Dysentery.—The seat of election of the typhoid bacillus is the lymphoid tissue of the lower portion of the ileum. The bacillus of dysentery, or more accurately the group of dysentery bacilli, affects specifically the colon, inducing here a diffuse ulcerative inflammation involving mucosa and submucosa, which unlike the colitis set up by the entamœba histolytica affects the descending and sigmoid regions to a greater extent than the cæcum and ascending colon. The rectum is also liable to be involved. Just as the colon may be affected in typhoid fever, so in bacillary dysentery the inflammation may extend into the lower part of the ileum.

It must be clearly understood that properly speaking "dysentery" is a symptom. A dysentery is any condition characterized by the painful passage of fluid blood-stained stools with mucous shreds, the indication of a hæmorrhagic colitis or proctitis.[1] Not a few organisms of different orders may be found sporadically causing this condition, but where it occurs either endemically or epidemically, either the entamœba or (more commonly in the temperate zone) a member of the group of dysentery bacilli is causative.

This bacillary dysentery shows itself as an infection with acute onset and low febrile condition, characterized by the frequent call to

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[1] πρόκτος (proktos), the rectum.

pass stools as above described. In very acute cases the loss of fluid and collapse is so severe that death ensues in a few days; in the non-fatal cases there is a slow lysis. The more extensive the ulceration the slower the healing, and the more prolonged the convalescence, so that certain cases assume a chronic type. Perforation is rare, but peritonitis from infection through the ulcerated areas is not infrequent.

In cases that are acutely fatal, the mucous membrane is found swollen, intensely congested and hæmorrhagic with prominent rugæ, the surface being covered with viscid blood-stained mucus. If death occurs somewhat later, the mucosa is found necrotic, grayish, and with a membranous exudate, particularly over the more prominent folds of the swollen mucosa. With this there are liable to be scattered areas of deeper necrosis in the form of brownish or blackish sloughs (stained by the fæcal pigment). The submucosa shows infiltration with pus cells. At a later stage there are extensive and numerous ulcers, tending to be transverse or circular, with undermined edges extending down to the muscle layer. In extreme cases the mucosa and submucosa over large areas may be sloughed off forming huge ring-like or band-like ulcers, an inch and more in extent from above downward. There are no markedly specific lesions in other organs.

Mucosus Capsulatus Infections.—In 1887 Bordone-Uffreduzzi described three cases of a peculiar septicæmia fatal in from two to four days with congestion and hæmorrhage of the internal organs. From each of these he isolated a capsulated bacillus pathogenic for mice, rabbits, and guinea-pigs. Since then many observers have encountered similar organisms in cases of hæmorrhagic septicæmia in man. Some have developed as a cryptogenic infection, in others the process has evidently started as a local infection. There is often a well-marked macular or petechial eruption, and the condition at times is that of an acutely fatal purpura hæmorrhagica. At autopsy, acute congestion with hæmorrhages of the gastric and intestinal mucosa, cloudy swelling of organs, and subserous and other hæmorrages in various organs are the main features. From the lesions there are to be gained plump rods, pleomorphic and capsulated, Gram-negative, non-motile, non-spore-bearing, not liquefying gelatin, growing easily on solid media, the colonies having a mucilaginous consistence, and on sugar-containing media producing so much gas that the organism has been described by some as the *B. aërogenes.* Occasionally indeed (possibly, as Welch has suggested, in cases of diabetes) members of this group of organisms lead to the production of gas cysts in the brain or generalized gaseous emphysema of the organs, with cysts in the lungs, liver, heart, kidneys, etc. One member of this group, a less active gas producer, is *Friedländer's pneumobacillus,* which is the cause of a small percentage of the cases of acute croupous pneumonia. In the one case of this condition observed by us—for bacillary pneumonia is not so frequent in North America as it appears to be in Germany—the distinguishing feature of the consolidated or hepatized lung was the curious glairiness of the

cut surface, a stringy mucoid exudate adhering to the knife. Hence evidently, according to the mode of infection, either pneumonia or bacteriemia with hæmorrhagic septicæmia is the main feature of the disease.

The Plague (Oriental Plague).—Among the lower animals severe epizoötics of hæmorrhagic septicæmia are set up by a group of closely allied small bacilli, short, almost oval forms, Gram-negative and with polar staining. The human representative of this group is the plague bacillus which, when it gains entrance through the respiratory tract, sets up both pneumonia and the most virulent and hæmorrhagic septicæmia known—the Black Death of the Middle Ages, which recently but for the prompt action of the American Commission would once again have spread from Manchuria throughout Asia and Europe.

As it is, the other more common type of plague is sufficiently fatal to have led within this generation to a huge mortality in China and India. Rats and other rodents, such as the ground squirrels and gophers of this continent, act as bacillus carriers. From causes unknown, the bacilli may after intervals of years gain in virulence and lead to epizoötics, in which when the animals die, their fleas may temporarily transfer themselves to any human being in the neighborhood. As a result of a flea bite the bacilli are conveyed by the subcutaneous lymphatics to the nearest group of lymph follicles. In bare-legged Oriental races the glands of the groin are most frequently involved. So with proliferation of the bacilli in the lymph nodes, there ensues an acute inflammation with great swelling or "*buboes*," the "emerods" of the biblical account of the plague among the Philistines.[1]

These buboes are the characteristic lesion of the disease. Puncture of the swollen nodes affords abundant bacilli. Rapidly the nodes become almost diffluent, with surrounding inflammatory œdema, followed by escape of the bacilli beyond these barriers, entrance into the blood-stream, development of a fatal bacteriemia, the bacilli being now recoverable from all the organs of the body.

Where the bacilli are inhaled into the lungs and set up pneumonia, there is not this lymphatic arrest. Not only is the bacteriemia more rapidly developed and more extreme, leading to cutaneous and other hæmorrhages; but in the act of coughing the bacilli are diffused into the atmosphere leading to a widespread infection of all who come into the immediate neighborhood of the patient. In recent years the Asiatic outbreaks of the pulmonary form were referred to, as pneumonic, distinct from the usual type of bubonic plague.

The Influenza Group.—The wide differences that may represent themselves in the lesions set up by a single species of organisms like the B. pestis, just described, will possibly prepare us to see little anomaly in bringing together conditions like influenza (la grippe), whooping cough, acute conjunctivitis, and canine distemper.

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[1] I. Sam., chap. V, v. 6.

Yet these are all conditions set up by organisms so similar morphologically and in their mode of growth, that they are difficult to distinguish one from the other. In each of these conditions we deal apparently with specific but closely allied bacilli—singularly small, Gram-negative, not growing in ordinary media, but needing for their growth outside the body the presence of either red-blood corpuscles or their essential constituent hemoglobin.

Whooping Cough.—Whooping cough is an epidemic condition characterized, as the name implies, by paroxysmal attacks of coughing, which so empty the lungs that at the close of the paroxysm air is drawn in with much effort and causes a crowing or whooping sound. The disease is rarely directly fatal. Bronchitis with thick mucus and bronchopneumonia are frequent accompaniments. The complete emptying of the lungs in infants may in the presence of the thick mucus result in collapse. The strain thrown upon the lungs may induce emphysema. In the early stages the expectoration contains abundant minute bacilli— the Bordet-Gengou bacilli. At autopsy in the rare cases that die during the course of the disease, no specific lesions are determinable save tracheal congestion; but if, as Mallory has demonstrated, sections be made of the trachea, a remarkable condition is found, namely, that immediately upon the free surface of the columnar epithelium, and actually between the fine cilia of the individual cells, are closely packed masses of the specific bacilli. Evidently it is the irritation set up by these that causes the cough. The bacilli, it seems, have only this local superficial growth, and they are not to be gained from the blood or internal organs.

Canine Distemper.—As demonstrated by our colleague, Dr. Rhea, the organisms occupy a position upon the tracheal mucosa identical with that just described for whooping cough. But unlike the whooping cough organism it may set up not merely bronchopneumonia, but may gain entrance into the blood, setting up a diversity of nervous and other symptoms, so various, indeed, as to resemble influenza.

Influenza.—La grippe is an epidemic and highly infectious condition, which, unknown for at least two generations, reappeared, sweeping across Europe from Eastern Asia in the early nineties, and, passing rapidly to the American continent, has since then been endemic. Judged from the variations in predominant symptoms in successive years, the specific organism either produces mutants, or is capable of considerable variation in its pathogenic properties; now respiratory disorders are the more frequent, now nervous, now digestive.

Evidently the infection is through the upper respiratory passages, the condition beginning as an acute coryza with running at the nose and eyes, with photophobia. Fever, backache, and muscular pains rapidly supervene, with or without indications of bronchitis, bronchopneumonia, enteritis, and other disturbances. After a few days the acute attack passes off, leaving behind great muscular weakness and a condition of lassitude from which there is slow recovery.

The nasal and pulmonary discharge in the early stages contains abundant bacilli. These also are to be gained from the blood at the height of the disease. It cannot be said that so far any specific lesions have been recognized.

Acute Conjunctivitis.—One form (and there are many) of epidemic acute conjunctivitis, characterized by intense injection of the bulbar conjunctiva, reddened œdematous lids, and profuse mucopurulent discharge, has associated with it an influenza-like bacillus, the Koch-Weeks bacillus. It will be observed that as an exposed moist surface, the conjunctiva is liable to be infected by a series of pathogenic organisms: the gonococcus, pneumococcus, pyococci, diphtheria and Morax-Axenfeld bacilli, etc. The Koch-Weeks bacillus has not been found setting up disease elsewhere in the system, nor is it pathogenic for lower animals. In infants McKee has found frequently another member of this group associated with catarrhal palpebral conjunctivitis. This form is pathogenic for mice.

Spirillar Infections.—The Cholera Group.—The group of diseases due to spirilla or vibrios is best treated here, since the remaining infections due to bacilli have associated with them organisms, which, either as being spore-bearing, or because they have the capacity to develop branching forms, are to be regarded as belonging to the higher bacteria. The mere fact that they are curved, and under exceptional conditions may produce definite spirals, is not sufficient reason for separating the vibrios from the rest of the lower bacteria.

Several closely allied vibrios, all motile, Gram-negative, gelatin-liquefying and non-spore-bearing have been isolated from water. Various strains differing in small details, such as pigment production, have been isolated from cases of true Asiatic cholera. Those regarded as typical possess a single polar flagellum, and these all afford the Pfeiffer reaction with the serum of animals highly immunized against the type Sp. choleræ (culture Berlin). One form, the V. massouæ, while obtained from what clinically was typical cholera in Abyssinia, possesses two terminal flagella, and is regarded as a distinct species. Another form, the Sp. Finkler-Prior, has been isolated from certain cases of the less acute cholera nostras or summer diarrhœa.

After a brief incubation period of a few hours, during which the organisms proliferate rapidly in the alimentary canal, the cholera spirilla induce an intense congestion of more particularly the small intestine with excessive discharge of fluid from the blood into the bowel, causing thus a diarrhœa which, after the discharge of the intestinal contents, becomes watery, consisting of little more than clear serum with shreds or small scales of the necrotic intestinal mucosa, the so-called "rice-water stools."

There is thus a rapid draft upon the blood, as well as all the body and tissue fluids. In order to preserve so far as possible the volume of the blood, so soon as this begins to diminish all the tissue spaces and the cells of the tissues contribute as much fluid as possible. The

result is a rapid shrinkage of the tissues; there is now seen the "facies Hippocratica" with sunken orbits and cheeks, and prominent cheek bones. The loss of fluid continues, until often so diminished in amount is the circulating blood, and so thick and tarry its nature, that pricking the skin affords no blood, and even upon cutting the finger there is scarcely any hæmorrhage. The heart beats become small and rapid, and the pulse imperceptible. So great is the drain that death may occur within a few hours.

At autopsy the main features are the dried-up character of the various organs, the thick, tarry blood, and the state of the intestinal mucosa. The spirilla have not entered the tissues. They have confined themselves to the intestinal mucosa, or at most have penetrated here and there to the superficial layers of the submucosa. The superficial mucosa has undergone necrosis and erosion, but on the exposed surface and in the crypts of Lieberkühn, and even between the lining cubical or columnar cells, the spirilla are to be detected.

The various tissues show cloudy degeneration. Owing to the very feeble production of recognizable ectotoxins in cultures made outside the body, it has been doubted whether the vibrios exert more than a local action. Relatively very large amounts of filtered culture fluids have to be inoculated into the animals of the laboratory to set up any serious results. Very recently the interesting observations of Penfold and Violle that the toxicity of culture fluids of the Sp. choleræ is greatly increased by high dilution with water has suggested that the very discharge of abundant fluid into the lumen of the intestine may be to the further detriment of the patient by exalting the action of the ectotoxins, which now may become absorbed through the denuded mucosa.

DISEASES ASSOCIATED WITH HIGHER BACTERIA

Diseases Produced by Spore-bearing Bacteria.—Anthrax.—This is the one disease produced by an aërobic spore-bearing bacillus in man, and, according to Vaughan, it differs from all other bacterial diseases in that, grown outside the body, the organism yields neither ectotoxins nor endotoxins of any virulence. If this be so, it nevertheless has to be admitted that gaining entrance through the skin and growing locally it induces a most intense local reaction, taking the form of a malignant carbuncle with rapid tissue necrosis and a surrounding zone of acute congestion and hyperæmia, while similarly when inhaled, in wool-sorter's disease, it induces an extensive and rapidly fatal pneumonia. Toxins there must be to produce these violent effects. The pneumonic exudate is not due to the mechanical blocking of the pulmonary capillaries with bacilli.

After the primary growth of the organism in the skin or pulmonary alveoli, the bacilli are liable to be carried into the bloodvessels by leucocytes, and once in the blood are apt to multiply with extraordinary rapidity, so that there is no disease in which a more extensive bac-

teriemia is to be observed. The blocking of the glomerular loops may lead to hematuria, of the submucous capillaries of the intestines to melæna. In the domestic animals enlargement of the spleen is very noticeable, hence the term splenic fever, and in them hæmorrhagic enteritis is very common. In these animals the bacillus is apt to set up severe epizoötics, with an animal mortality at times which makes its economic importance of great moment. Fortunately the disease is rare in man, and almost confined to sporadic cases of infection among those who handle hides, hair and wool coming from infected regions.

Due to Anaërobic Spore-bearing Bacilli.—The most notorious but not the commonest anaërobic spore-bearer causing disease in man is the **tetanus** bacillus. This is a frequent if not a regular inhabitant of the intestines of the horse, and infection in man is specially associated with the stable, with street and garden earth. The spores have great powers of resistance. It is when contaminated earth gains entrance to a wound that infection is liable to ensue. There are those who hold that the spores pure and simple may set up disease in man; but if so, this is the exception. The conditions which favor the onset of tetanus are (1) the infliction of a deep wound or a pocket of skin whose recesses are cut off from the outer air, (2) the contamination of the instrument inflicting the wound with earth or matter from stable, street, etc., (3) the growth within the wound of a mixture of aërobic and anaërobic organisms. The aërobes by using up the oxygen in the neighborhood evidently favor the growth of the anaërobes.

The other outstanding features of the tetanus bacillus are these (1) that the growth is purely local within the wound: cultures may occasionally be obtained from the spleen and other organs, but the colonies are so infrequent as to indicate that while the bacilli may be transported to these other organs, they do not multiply within them; (2) that it produces a most powerful ectotoxin. As shown by several observers the tetanotoxin has a peculiar affinity for nervous tissue, and what is more, as shown by Meyer and Ransom, the toxin reaches the higher centres not so much by means of the blood as along the peripheral nerves. As in rabies so here, the incubation period, the time between entrance of the microbes into the tissue and the onset of active symptoms of nervous disturbance, depends upon the distance of the region of injury from the nerve centres in the cord and brain— depends upon the length of the path the toxins have to traverse before reaching the bodies and nuclei of the motor nerve-cell bodies. Once the toxins reach these they cause intense irritation, as a result of which the muscles governed by these cells are thrown into a state of spastic contracture (tetanus). Once the toxins reach the cord or brain they diffuse and affect other motor centres. The intense contraction of the muscles is accompanied by increased heat production and high fever, and if death does not occur through contraction of certain respiratory muscles, the nerve cells pass from a state of overstimulation to one of exhaustion, apt to be mistaken for recovery. The Nissl bodies of the

nerve cells have been found disintegrated and used up, the nuclei with diminished chromatin and shrunken.

Diphtheria.—Diphtheria bacilli and the forms most nearly allied characteristically proliferate in the upper respiratory passages, the nares, pharynx and trachea, not gaining entrance into the tissues to any marked extent. Other diphtheroid bacilli apparently not so closely related, are being described with increasing frequency as being isolated from the intestine, the lymph nodes, the brain, and other internal organs in more chronic conditions, in most of which it seems they are not to be regarded as causative agents. As a group these bacilli are irregular in breadth as well as length, non-motile, non-spore bearing though often exhibiting metachromatic granules, Gram-positive, and not liquefying gelatin. At times, grown outside the body, definitely branching forms develop.

Of the diphtheria group proper, we may dismiss Hoffmann's bacillus, present frequently in the throat, and the Xerosis bacillus, extremely common in the conjunctiva and so passing with the lacrimal fluid into the nose, by saying that while if care be not taken, they may be mistaken for the diphtheria bacillus, they produce no known disturbances. The latter, while it varies widely in the virulence of different strains, produces well-marked lesions, varying somewhat according to locality.

It deserves note that the lesions produced by the diphtheria bacillus vary according to the region of growth. Thus nasal diphtheria is characterized by the development of a prolonged catarrhal condition with relatively slight febrile and general bodily disturbance, and without the formation of membrane. The discharge contains abundant bacilli, and is distinctly infectious. The characteristic lesion is produced when the bacillus gains a growth in the throat. This most frequently begins upon one or both tonsils, showing itself in the form of dirty whitish plaques, which, spreading, are apt to cover the pharynx, and thence may extend over the walls of the larynx, and in severe cases may involve the trachea and affect even the smaller bronchi.

The nature of this inflammatory ("false") membrane is essentially that of a fibrinous exudate. The growth of the bacilli upon the surface causes a necrosis of the epithelium which affects the whole thickness, be it a squamous or a columnar epithelium. In the former case it tends to involve also the superficial layers of the subcutaneous tissue, and as the irritation simultaneously causes an intense congestion, with pouring out of serum and leucocytes, and as the exudate undergoes coagulation, so covering over the denuded surface, there is formed a somewhat dense leathery membrane. This fibrin formation and deposit involves also the necrotic tissue, and as at first this is not sharply demarcated from the underlying living tissue, attempts to remove the membrane are apt to tear and pull away the outer layers of the greatly congested living tissue and cause hæmorrhage.

At a later stage abundant leucocytes invade the necrosed tissue, forming a well-marked layer between the fibrinous membrane and the

living tissue. These dissolve the deeper fibrin, and bring about destruction of the bacilli. In this way, as healing sets in, the membrane becomes loosened and finally cast off. In the trachea with its columnar-celled mucosa, the presence of a well-formed basement membrane appears often to prevent the extension of the necrosis into the submucosa, so that in general the membrane is not so firmly attached. But where the membrane forms a complete cast of the tracheal tube, and especially where this is firmly adherent in the larynx, it will be readily understood that the very loosening of the cast may bring about extreme obstruction to both expiration and inspiration. In the days before antitoxin treatment, suffocation and death from tracheal extension was the complication most to be feared.

The growth of the bacilli is essentially local; a few bacilli may be carried into the neighboring lymph nodes, and more rarely cultures may be gained from more distant organs or from the blood, but there is no active growth of such bacilli. While this is the case, there is diffusion of the ectotoxins absorbed from the affected surface, and this leads to well-marked cloudy swelling of the organs (see p. 268), and particularly is apt to influence the nerve tissues, setting up slowly transient paralysis of the muscles of the fauces, limbs, etc., days and it may be even weeks after disappearance of the false membrane. Where the vagi are affected, there may be sudden death from arrest of the heart action. The most notable feature of these partial paralyses is that the toxins affect the peripheral nerves in their continuity, here and there leading to the erosion of a limited area. In fatal cases it is seen that the nerves passing to a paralyzed area exhibit portions in which for a short distance the medullary sheaths are degenerated and the axis-cylinders frayed out and dissolved, while other fibres of the same nerve may be unaffected. This explains why paresis—incomplete paralysis—is more common than complete paralysis. Examination of the lymph nodes shows that these also are affected by the toxins: the cells of the germinal areas are found swollen, and in severe cases the degeneration passes on to their breaking down and dissolution, while the endothelial cells of the lymph sinuses likewise are large and prominent.

Infections by Diphtheroid Bacilli.—Of recent years, with increasing frequency, there have been observations upon the presence of bacilli, either of irregular shape like diphtheria bacilli, or beaded and presenting metachromatic granules, obtained from the internal organs in various conditions. In most cases further investigations have indicated that these are not the essential pathogenic agents. In Hodgkin's disease, or at least in an important group of cases included under this name, the proof at last appears to be almost complete, the organisms having been gained in pure culture and vaccines made from them having been found to exert a specific action in bringing about cure or at least betterment.

Hodgkin's Disease.—Hodgkin's disease or, as some prefer to term it, **infective lymphogranulomatosis,** is a disease characterized by progressive

enlargement of groups of lymph nodes, beginning most often in one group such as the deep cervical, and gradually involving others, until the affected nodes form huge packets, the individual nodes not only undergoing fibrosis of a chronic inflammatory type, but also being apt to become bound together by inflammatory fibrous tissue. The spleen also often attains great size. With this fibrotic destruction of certain nodes, others undergo a compensatory development and enlargement, hence the packets continually increase in size, until by pressure upon important passages and vessels they cause death.

FIG. 62
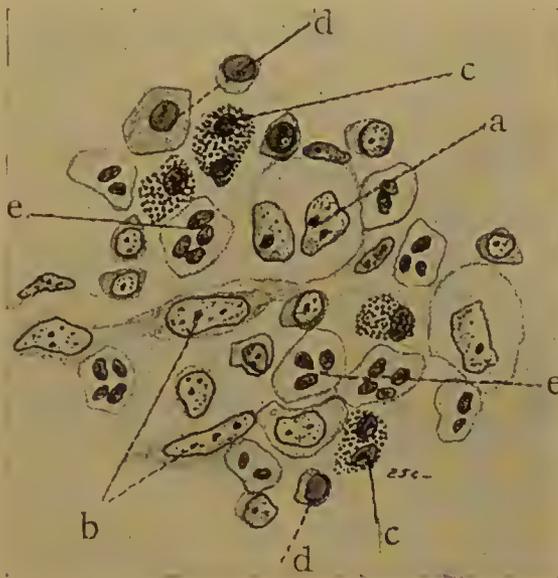
Section from a lymph node in Hodgkin's disease, showing the different orders of cells: *a*, degenerating leucocyte; *b*, fibroblast; *c*, eosinophile; *d*, lymphocytes, large and small; *e*, polynuclears.

Some few years ago Fränkel and Much called attention to certain Gram-positive granules—"Much's granules"—which are to be found in preparations made from the affected lymph nodes. At times these are to be seen in rows, evidently within bacillary bodies. Many have regarded these as beaded and attenuated tubercle bacilli. Indeed, the evidence is very strong that a fair proportion of the cases regarded clinically as Hodgkin's disease are truly a form of chronic lymphogranulomatosis set up by attenuated tubercle bacilli. But while this is so with the majority of cases exhibiting these granules, it has been found impossible either to set up tuberculosis in highly susceptible animals like the guinea-pig, or to gain cultures of the tubercle bacilli. On the other hand, recently upon this continent, Bunting has gained from several cases pure cultures of a diphtheroid bacillus. The organism at first shows growth only after several days and then under conditions of partial anaërobiosis; later it grows more freely and under aërobic conditions. These observations have been confirmed by Rosenow, Rhea, and others, and what is more, arrest of the disease and progressive reduction in the size of the lymph nodes have been observed following the use of vaccines made from the diphtheroid bacilli. These observa-

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tions confirm the view that Hodgkin's disease is not a form of new growth or hyperblastosis, but is an inflammatory overgrowth of the lymphoid tissue.

Tuberculosis.—While the characteristic lesion set up by the tubercle bacillus is the tubercle, it is well to remind the student at the outset that according to (1) the virulence of the bacilli, (2) the susceptibility of the individual, and (3) the region affected, there may be great variations in the lesions induced, from active suppuration on the one hand, to a diffuse productive and fibrotic change on the other. The tubercle, as it were, occupies a mid-place in the series; it is the commonest, most typical outcome of infection by the tubercle bacillus.

We have to regard the tubercle bacillus as possessing virulence of a peculiar order. It produces no ectotoxins, even under the most favorable conditions, outside the body: within the body it grows and multiplies slowly, while such is the nature of the bacterial body that it is acted upon with difficulty by the cells of the organism and their products. Thus its disintegration and the liberating of its endotoxins is a gradual process, and often even in the immediate neighborhood of bacilli undergoing lysis the concentration of the diffused toxins is so slight as to stimulate cell-growth rather than cause cell-death. Lastly, the toxins are such that they attract lymphocytes rather than polynuclear leucocytes.

Fig. 63
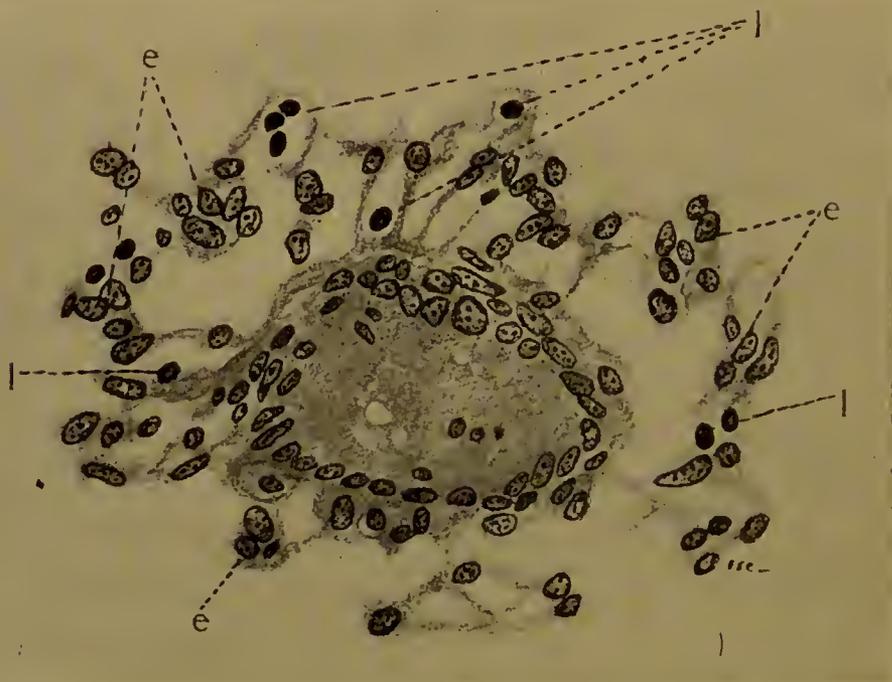
Giant cell from centre of tubercle, showing processes and peripheral arrangement of nuclei, and surrounding endothelial cells (*e, e*) and occasional lymphocytes (*l, l*)

The experimental production of tubercles by intravenous or other inoculation of tubercle bacilli, whether living or dead, shows that the bacilli at first taken up by cells of endothelial type do not lead to their immediate destruction. After a few days it is evident that these first

cells have been killed, but their remains are surrounded by swollen
and proliferated cells of connective-tissue type, together with a moderate
accumulation of lymphocytes. This forms the primordial tubercle,
too small to be recognizable by the naked eye. Often the fibroblastic
or "endothelial" cells immediately around the central debris fuse
together, so as to form what is truly a "foreign body giant cell," *i. e.*,
a multinucleated plasmodium or syncytium, the fused peripheral cells
with their nuclei forming a fence or enclosure within which is the finely
granular cell débris containing such bacilli as have survived the diges-
tive action of the earlier cells. There is evidence that where the bacilli
are upon mucous surfaces or within gland tubules, the epithelial cells
also are liable to fuse and form similar giant cells.

FIG. 64
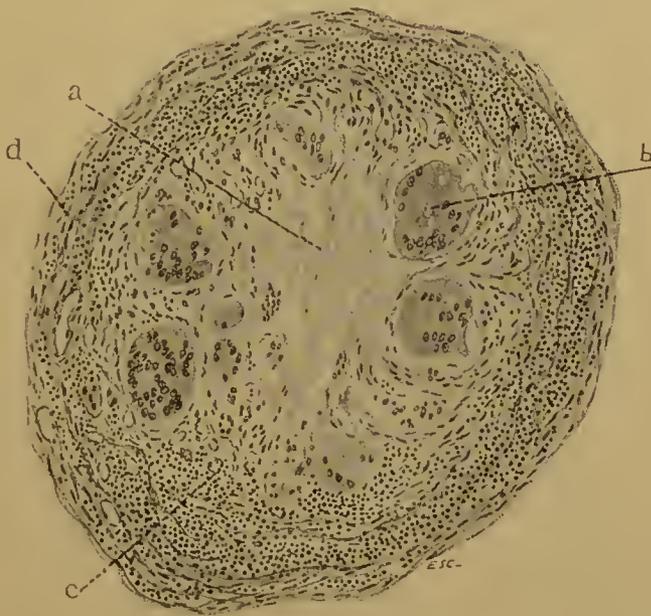
Tubercle from a case of tuberculosis of medium severity of the lung; *a*, central caseation; *b*, a
giant cell; *c*, endothelial cells; *d*, connective-tissue zone infiltrated with lymphocytes.

Accepting the view that the production of ectotoxins by tubercle
bacilli is negligible, it is, we confess, difficult to gain a clear picture
of the succession of events in the further development of the tubercle,
for that further development demands on the one hand, continued
proliferation of the bacilli, and on the other progressive destruction
of the same to yield the endotoxins. We can only imagine that just
as in an engagement between two hostile armies, the casualties are not
all on the one side, and the victorious army makes its way forward
only at the cost of many dead; so with the tubercle bacilli while some
proliferate, others are destroyed. Certain it is that we can make out
a progressive increase in the central necrosed area, with simultaneous
growth and accumulation of cells at the periphery, until the mass is
visible to the naked eye as a "miliary" tubercle. Generally in this early
stage the cell reaction is not sufficient to afford an impenetrable fence
around the bacilli: some pass out into the surrounding lymph spaces,

carried, it seems, by wandering cells, and there growing initiate the formation of new tubercles in close apposition to the old. With these the mass increases markedly in size, and is surrounded by a zone of daughter tubercles. As it is extravascular, no vessels penetrating into a tubercle, the next stage exhibits the whole area of the primordial tubercle affected by the necrotic change, and undergoing "caseation." The toxins, that is, when sufficiently concentrated, lead to a fatal and fatty degeneration of the cells, and the dead cells lose their outline, what is left being a homogeneous finely granular cheesy (caseous) matter.

Fig. 65
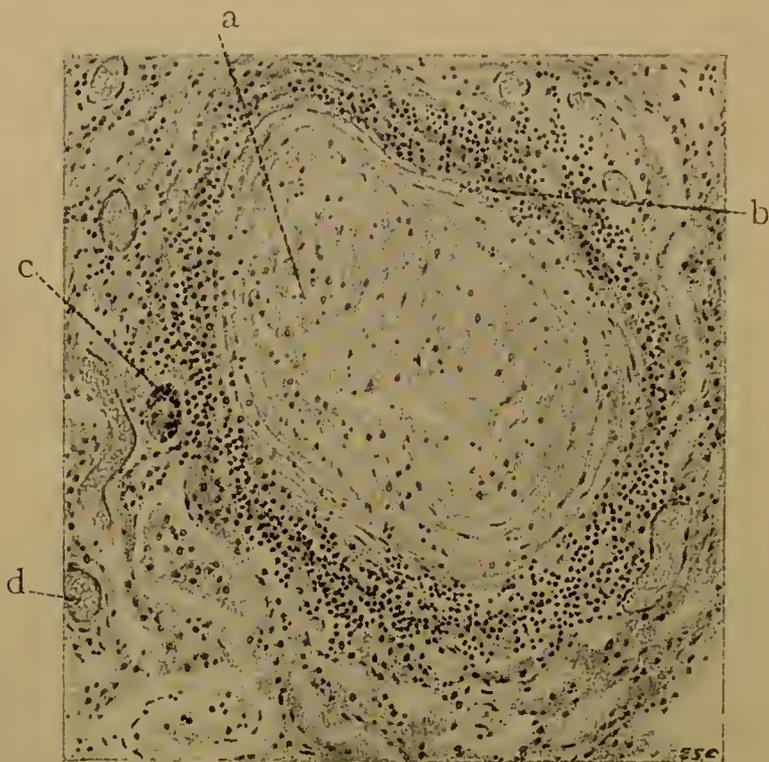
Section through early apical tubercle, showing: *a*, central caseation; *b*, surrounding cellular infiltration with fibrosis; *c*, giant cell; *d*, congested capillary outside tubercle, the tubercle itself being devoid of vessels.

Subsequent events vary according to circumstances. I. Either the diffusion of the toxins into the surrounding healthy tissues and the blood-stream may lead to the production of antibodies and an increased general resistance, or it may happen that by rest and improved environment the general resistance becomes raised. In either case the result may be that the reaction in the area immediately surrounding the area of bacillary proliferation becomes more effective. This shows itself by the formation of a well-marked zone of connective-tissue growth—of active formation of fibroblasts which, developing into connective-tissue cells with their fibrils, form a firm capsule, cutting off and enclosing the caseous matter and the bacilli and arresting further advance. This is not absolute healing, for the bacilli may remain alive in a latent state for years. It is common to meet these *obsolescent* or *obsolete* encapsulated areas in the lungs at autopsy. Observations upon a dog

with peritoneal tuberculosis indicate that small fibroid tubercles may eventually undergo complete absorption.

II. Or the reaction on the part of the tissues may be inadequate with, as a result, progressive local extension and increase of the caseous area, complicated by:

1. Carriage of the bacilli along the lymph spaces and by lymph vessels to new foci, either in the immediate neighborhood or at a distance.

2. Formation of a tubercle or tubercles in the walls of a bloodvessel with degeneration of the same, ulceration, and liberation of bacilli into the blood stream. The bacilli may thus be carried into the capillary areas throughout the body, and becoming arrested, may set up a universal tuberculosis. Where this occurs, the abundant proliferation of the bacilli and liberation of their toxins sets up an acute febrile disease, with rapid emaciation and death in a few weeks before the tubercles attain any great size—the condition of **hematogenous miliary tuberculosis.**

Fig. 66
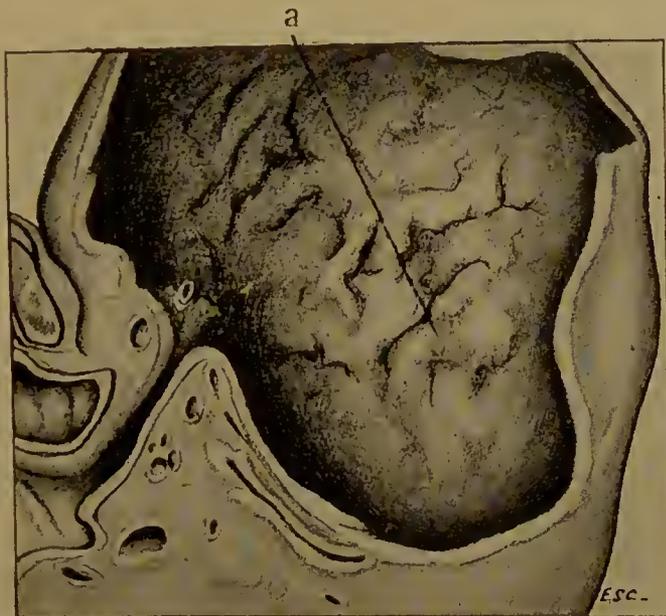
Tuberculous cavity (*a*) at apex of lung, showing its relation to a bronchus. (Pathological Museum, McGill University.)

3. Necrosis and ulceration of a conglomerate mass of tubercles situated immediately beneath a surface, with discharge of caseous matter containing the bacilli either immediately or mediately to the exterior of the body. This may happen in the case of:

(*a*) Cutaneous tuberculosis, *e. g.*, lupus of the face.
(*b*) Tuberculosis of the larynx and upper air passages.
(*c*) Tuberculosis of the lungs.
(*d*) Tuberculosis of the intestines.
(*e*) Tuberculosis of the bile passages and liver.
(*f*) Tuberculosis of the kidneys and bladder.
(*g*) Tuberculosis of the prostate, uterus, etc.

In the case of tuberculosis of the lungs ulcerating into a bronchus,

the result of the progressive discharge of the caseous matter is **cavitation**, *i. e.*, the production of a cavity in the organ, lined by cheesy matter. In this way, by the progressive lymphogenous production of tubercles and their caseation the entire lobe of a lung may be converted into a cavity. The same process may occur in the kidney, which may become represented by a multilocular sac, and to a less extent in the liver in bile-duct tuberculosis. In all these cases the discharge of the bacilli into ducts favors infection and the production of tubercles, and subsequently of ulcers along the course of these ducts. This, indeed, is the most important factor leading to the extension of respiratory and particularly of pulmonary tuberculosis.

Leprosy.—Although leprosy is one of the most ancient of known diseases,[1] and the lepra bacillus was one of the first among pathogenic bacteria to be clearly recognized (by Hansen, 1871), there still remain more matters to be elucidated in connection with this than with most other diseases. We still, for example, are uncertain how the disease is communicated from individual to individual, and although by now many observers have announced the successful isolation and cultivation of the bacilli, the descriptions afforded and the actual cultures sent out vary so considerably among themselves that it is uncertain which is to be regarded as the type organism, which a contamination or chance invader of the affected tissues. Some observers employing special methods, like Clegg and Duval, have so frequently gained cultures from cases of this disease, and that of forms with properties different from those of any bacteria hitherto studied, that it is difficult not to believe that they have the specific organism, more especially when one stage in the development of these cultures affords acid-fast forms resembling those seen in the lepra nodules, and by the inoculation of such cultures a disease resembling leprosy has been produced in the monkey and the Japanese dancing mouse. But when the same observers at times obtain chromogenic organisms, at others colorless cultures, and regard these as distinct, and proceed to dispute among themselves as to which is the disease-producing species, there is nothing to be done but wait for more decisive investigations.

In the meantime this may be said definitely, that leprosy is, in general, a slowly progressive disease of the nature of an infectious granuloma, which, causing grave disfigurement, may be present for many years before death ensues. More acute cases are encountered, but these are rare. Two main types are recognized: (1) the *nodular*, in which the lepra tubercles or nodules specially affect the dermis of the face and extremities, and it may be also the mucous membranes, and (2) the *anæsthetic* or smooth, in which the nodules form along the course of peripheral nerves, and by gradual destruction of these peripheral nerve trunks bring about areas of local anæsthesia and dry gangrene, so that

[1] Prescriptions for the cure of what is evidently this disease are given in the Ebers papyrus (1348–1281 B.C.) and these date back to the First Dynasty, 4600 B.C.

digits and other parts undergo atrophy, death, and separation. But the two orders of lesions may coexist. In the cutaneous type the epidermis may become involved, with a low form of ulceration. In both types microscopic examination of the affected tissues reveals the presence of tubercles. In the nodular type it is the corium that is specially affected, the process beginning apparently in the middle or deeper layers, the overgrowth extending into the upper and papillary layers, so that the papilla becomes thinned and slow ulceration may result. The affected area shows increased connective-tissue growth infiltrated with characteristic large cells, which upon proper staining —namely, by acid-fast stains—are seen to contain enormous numbers of thin beaded bacilli of the B. tuberculosis type.

The bacilli are found free and often massed along the course of the lymph channels. The lepra cells are in general larger than ordinary leucocytes, often four or five times larger. Occasionally giant cells may be detected. With this there is marked endothelial proliferation of the arterioles of the part with the condition of arteritis obliterans and pariarteritis. The capillaries also show endothelial proliferation, and the "lepra cells" are of endothelial origin. In the anæsthetic type the diseased nerve shows fusiform swellings along its course, these swellings exhibiting infiltration with frequent "lepra cells," together with a condition of chronic perineuritis, fibrosis, and degeneration of the axis cylinders. Coincidentally the lymph nodes may be affected, becoming swollen, while in some cases there has been described sclerosis, as also meningitis of the spinal cord, although these are not essential changes. The lesions are of extremely chronic type: cases of anæsthetic leprosy of forty years' duration have been described.

Nodular (tubercular) leprosy involving the face and arm. (Todd and Wolbach, Gambian expedition.)

It has been noted by several observers that not all the bacilli in the lepra nodules are acid-fast. Particularly in young nodules lepra bacilli lose their stain after immersion in weak acid, and can then be colored by Löffler's blue. This harmonizes with the description of Bordone-Uffreduzzi, who apparently first succeeded in cultivating the organism, and of Duval and of most recent observers regarding the forms cul-

tivated outside the body. The organism at first stains by ordinary methods, only later becoming acid-fast.

It is evident that ordinarily the disease is communicated from individual to individual with great difficulty. Thus in the Trinidad Asylum it has been noted that the Dominican nursing Sisters had been in constant contact with the lepers for thirty-six years and not one of them had become infected; yet contact with the lepers for some years, as in the case of Fathers Damien and Gregory, in Molokai, may result in the contraction of the disease. One case is recorded in which close contact with a leper for two months resulted in infection. Whether the disease is communicated by insect carriers or through cutaneous lesions is undetermined.

Fig. 68
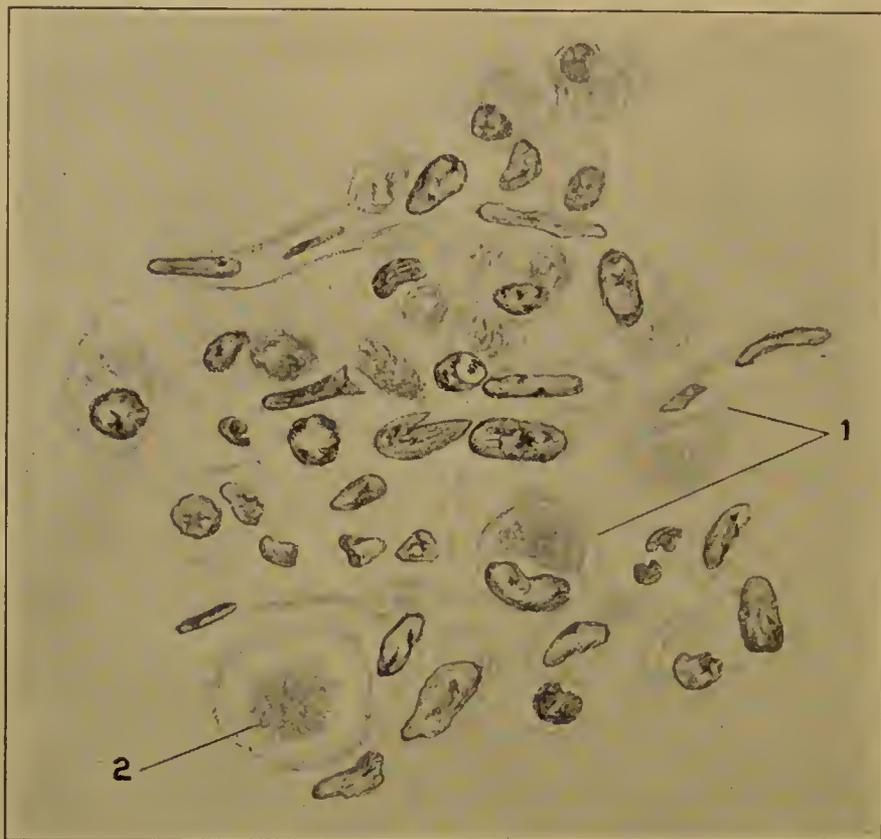
Lepra nodule in omentum of Japanese dancing mouse inoculated with culture from case of leprosy in man. Note the "lepra cells," filled with bacilli, and the scattered free bacilli. 1, cells of endothelial type swollen and containing the lepra bacilli; 2, cell so packed with bacilli that it has undergone necrosis and is about to rupture. (After Duval.)

Rat Leprosy.—Stefansky and Dean, in 1903, independently reported the existence of a disease in rats resembling leprosy in which the cutaneous and lymphatic nodules exhibited the same abundance of lepra cells containing acid-fast bacilli. From these lesions a diphtheroid bacillus has been with difficulty cultivated, resembling in most respects the cultures gained from human leprosy. Using the affected tissues from the rat as antigen the complement-fixation test is gained with

human leprosy patient's serum. This indicates close relationship, if not identity between the causative microörganisms.

Glanders.—It is difficult to know where to place glanders if not in this group; for although most often in man an acute disease, in its usual host, the horse, it is frequently of chronic type; it has a tendency to spread by the lymphatics; the glanders nodules, although of looser, less cellular nature with more exudation ("farcy oil"), are of tubercle-like character. In the horse also the lesions may become fibrotic and arrested and the disease rendered latent rather than truly healed; the animals may become "ceased reactors," not reacting to mallein (the homologue of tuberculin). Nevertheless the disease may light up again from the old foci. In other words, just as tubercle bacilli may remain latent in obsolescent fibrotic tubercles, so the glanders bacilli may retain their vitality for months and years in old fibrosed glanders lesions. Saying this, it must be remembered that there is a wide difference between the causative microbes; the glanders bacilli thrive as easily and rapidly on various media as the tubercle bacilli grow with difficulty; they take up and liberate dyes with as much facility as the tubercle bacilli are stained and decolorized with difficulty.

In the horse the common site of infection is through the nasal passages; most commonly a local "chancre" forms and ulcerates upon the nasal septum. In man also the earliest lesion presents itself most often along the respiratory tract, either in the form of ulcers with acute congestion of the nasal mucosa, or of bronchopneumonia. But both in the horse and in man, infection may also occur through the skin.

In the horse the most destructive lesions are encountered in the lungs in the form of scattered, rather coarse tubercles, each surrounded by a zone of acute congestion and pneumonia. In the recent glanders tubercle the centre is formed of a collection of polynuclear leucocytes, often with broken-down pyknotic nuclei. As this centre grows older and larger it takes on a yellowish or whitish color. External to this is a zone of endothelioid cells surrounded by a second zone where pneumonic exudate has occurred into the alveoli. In less acute cases the pneumonia is replaced by a capsule of fibroblastic and connective-tissue formation. The necrotic centre may indeed undergo calcification. In man there is what appears as a patchy lobular pneumonia with purulent breaking down central regions, the tubercular process not being so obvious.

Both in the horse and in man we at times encounter the cutaneous or subcutaneous form of the disease, termed **farcy.** In the horse this is of the nature of a lymphangitis with swollen inflamed lymphatics along which occur swellings, the so-called "farcy buds." We doubt whether what is called farcy in man is of the same nature. This presents itself in the form of scattered small abscesses with a liability to ulcerate and discharge a blood-stained purulent fluid. The condition here appears to be more of the nature of a bacteriemia or pyemia, because simultaneously there may develop similar lesions in the kidneys, liver, muscles, etc. This more acute disease in man is attended with fever and the

development of a typhoid state, and is frequently fatal in from eight to fourteen days.

Streptothricosis.— Bollinger, of Munich, in 1877, first determined that the condition of lumpy jaw in cattle—a condition hitherto regarded as sarcoma or osteosarcoma—was due to the fungus-like parasite which from the radiate arrangement of its peripheral hyphæ he termed **actinomyces**—the ray fungus. It was left to Israels, a few years later, to recognize the disease in man. That it is not particularly uncommon is indicated by the fact that at one hospital in Montreal, in the course of little over ten years, more than forty cases have afforded the parasite.

Fig. 69
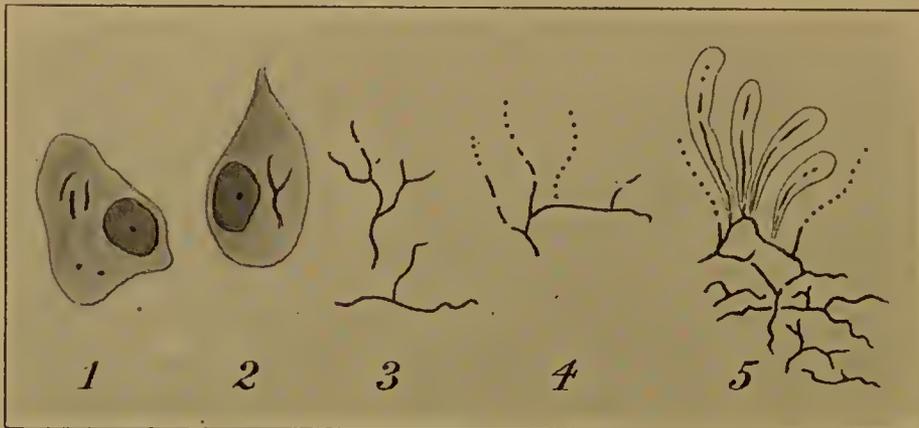
Stages in the development of actinomyces.   1 and 2. The earliest forms noted are often intracellular, cither bacillary or showing a single branching. 3 and 4. As the branching, mycelial threads grow and become longer they are apt to exhibit segmentation and thus cause peripheral branches, or more particularly, exhibit coccoid gonidia. 5. The typical ray fungus mass shows a swelling of the sheaths of its peripheral filaments, thus forming the characteristic "clubs;" occasionally there project between these unaffected strings of gonidia or filaments bearing gonidia.

In the course of years several allied species of filamentous forms with lateral branching have been isolated from distinct diseases in man and animals, and as not all of these exhibit the rayed arrangement, the generic name of **Streptothrix** has in America and England gradually come to replace the earlier Actinomyces. Today streptothricosis is synonymous with actinomycosis. If the spores (gonidia) of an old culture of any member of the genus be planted in broth, it is seen that these germinate in the course of a few hours, giving off one or more filaments, which in their turn give off lateral branches. These elongate and give off branches in their turn. Later these branches are apt to segment into bacillary lengths, while more particularly the terminal branches or minute hyphæ form within themselves chains of coccus-like gonidia. In the tissues these terminal hyphæ, in actinomycosis proper and in mycetoma pedis, are apt to undergo a protective thickening, so giving rise to the peripheral coarse rays or clubs. It should be added that cultures of non-pigment-forming species closely resemble those of B. tuberculosis, while some (S. nocardi and S. eppingeri) are acid-fast.

Besides actinomycosis proper (the lumpy jaw of cattle) the following diseases have been found to be caused by streptothricæ, namely, human actinomycosis, bovine farcy (farcin de bœuf) set up by S. nocardi, mycetoma pedis, or Madura foot, from which Vincent isolated and grew S. maduræ. Other streptothrical diseases have been determined in fowls, goats, horses, the cat, and other mammals. In man, according to Foulerton, there are several pathogenic species including not only those inducing granulomatous lesions, but others, like S. eppingeri, found associated with cerebral abscess and multiple miliary abscesses in the lungs, kidneys and other organs.

While in cattle the ray fungus sets up a chronic, well localized granulomatous change with much fibrosis around and between the individual agglomerated tubercles, in man the condition as a rule is more acute. Infection most often originates in the mouth, at times the primary lesions are in the lungs, intestines (appendix), liver and brain. In the last two cases it is most probable that there has been a primary lesion within the digestive or respiratory tract, which has undergone healing. In the lungs the lesions often simulate tuberculosis; the most typical lesions are in the liver. The affected area has a characteristically spongy appearance; a fibrous stroma separates areas of softening and suppuration. The matter filling these contains granules like millet seeds, which under the microscope are seen to be colonies or tufted mycelial masses, with the peripheral radiating clubs which are recognizable even by the lower powers of the microscope. Infection may spread along the lymphatics to neighboring organs. Beyond the local growth and reaction there is little general disturbance.

DISEASES DUE TO FILTERABLE VIRUSES

By the demonstration that infection may be brought about by the use of filtrates through porcelain filters, we now recognize that several important diseases are induced by organisms so minute that even under the highest power of the microscope it is difficult to determine their morphology. These diseases we may divide into two or more groups—namely, (1) the specific exanthemata, smallpox, vaccinia, chicken-pox, scarlet fever, and probably measles, rötheln (by analogy); (2) rabies, acute poliomyelitis, and yellow fever. Many other diseases of the lower animals give these filterable viruses, notably contagious pleuro-pneumonia of cattle, which was the first to be studied and recognized; these need not here detain us.

In the characteristic lesions of the first group are involved the skin, mouth, and pharynx, and to a less extent other mucous membranes. In connection with smallpox and scarlet fever, more particularly, the tonsils are found enlarged and inflamed, and so frequently is there an associated growth of streptococci that several observers have regarded these as the essential cause, a view which must be regarded as incorrect,

since inoculation of pure cultures of streptococci isolated from cases of the diseases uniformly fail to reproduce the characteristic lesions.

FIG. 70
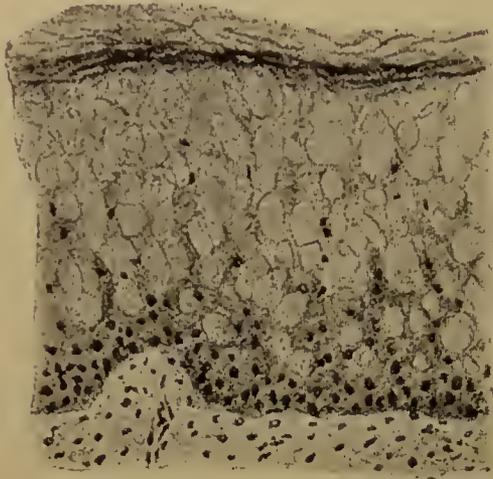
Smallpox: hydropic degeneration of epithelium from a papule; the epidermal cells greatly swollen, distended by large vacuoles. × 300. (Ribbert.)

The distribution of the lesions suggests that the causative agents thrive best in a temperature lower than the normal body heat. After a period of incubation (possibly in the tonsils or pharynx), there is a stage in which these organisms gain entrance to the blood stream, and so are carried to the subcutaneous tissues. In the study of the characteristic skin lesion of smallpox it is noteworthy that this begins in the deeper layers of the epidermis, and that the vesicles are caused by an extraordinary dropsical degeneration of the prickle cells, leading to their necrosis and rupture.

In rabies and acute poliomyelitis the characteristic lesions involve the central nervous system. The hypothesis that poliomyelitis is a specific infection of the anterior horns (gray matter) of the spinal cord has been abandoned. Lesions occur regularly throughout the structures

FIG. 71
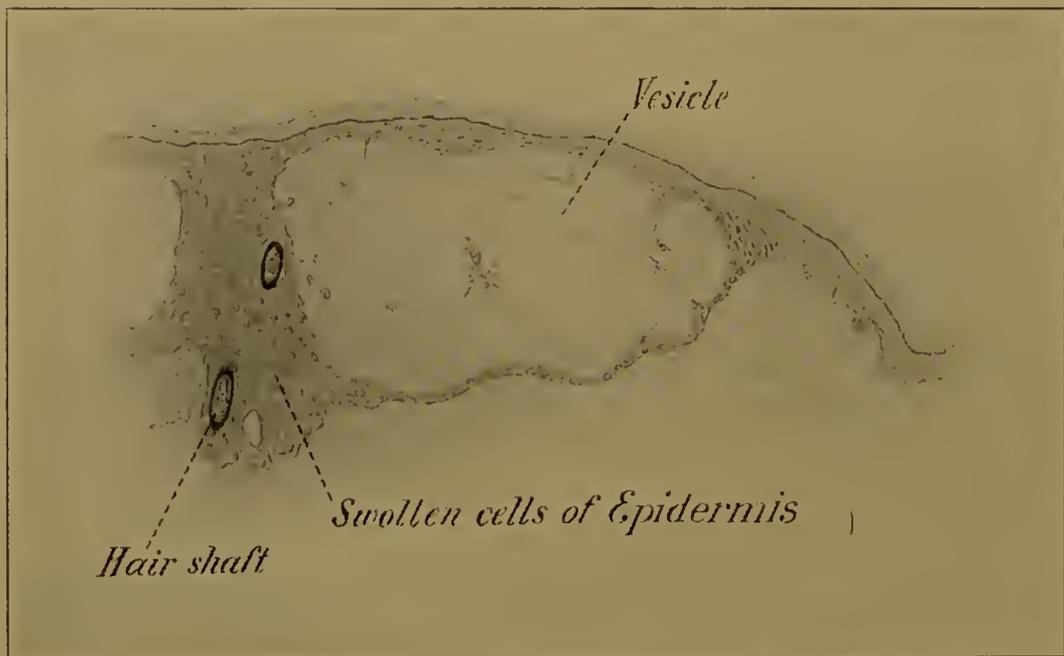
Section through a smallpox vesicle, to demonstrate its development as a hydropic degeneration of the epidermal cells. Nuclei and other debris of the greatly swollen and broken-down cells can be seen within the vesicle. (Prof. Rhea.)

of the cord and posterior ganglia, frequently in the medulla and brain, and quite often, as shown by Flexner and his associates, in the Gasserian

and abdominal sympathetic ganglia. The pia arachnoid membranes are constantly involved. It would appear that the virus passes hence along the fibrillar supporting tissues and small bloodvessels into the substance of the brain and cord. One of the most characteristic lesions is found along the blood vessels around which are found diffuse or nodular accumulations of mononuclear cells. Globoid bodies, at times in small masses, at times in short chains resembling extraordinarily minute cocci, have been cultivated from the central nervous organs of human beings and monkeys, and may be detected in the incubated brain tissues of infected monkeys. Thus epidemic poliomyelitis may be regarded as a disease in which the organisms have a special affinity to the nervous system, although the most prominent and important symptoms are those following injury to the motor neurones of the cord and brain. The degree to which the nervous cells are destroyed is variable. Experimentally it has been found that when intrasciatic injections are made, the virus travels to the spinal cord by the lymphatic channels, and brings about paralysis, at first on the side of injection, and later upon the opposite side.

In *rabies* it is interesting to observe that the course of events is similar to what has been determined experimentally in poliomyelitis, namely, the characteristic lesions are cerebral, but the ordinary path by which the virus reaches the brain is along the nerves, presumably by their lymphatics. The farther removed is the site of infection from the brain, the longer the period of incubation, for which reason bites upon the face or head are most dangerous. In rare cases it may happen that there is at the time of the bite direct inoculation of the blood. The characteristic lesions found in this disease are in the ganglion cells of the bulb, as also in the spinal ganglia. The nerve cells here are distinctly degenerated with chromatolysis and even total disappearance of the nuclei, with dilatation of the pericellular spaces and invasion of the same by mononuclear cells. In certain nerve cells of the cerebrum, cerebellum, pons, and basal ganglia, Negri first called attention to the existence of the presence of rounded bodies varying in size from 4 to 15 μ. There is still debate as to the nature of these bodies. Lambert, for example, in his attempts to induce their growth, by cultivating nerve cells containing them *in vitro*, notes that he obtains similar bodies in normal nerve cells thus treated. An increasing number of observers, however, appear to favor their parasitic nature.

DISEASES CAUSED BY THE HIGHER FUNGI

Blastomycosis.—Yeasts.—There are various orders of moulds (the yeasts while related, are regarded as a class apart) larger than bacteria, but like them multiplying only asexually; they grow by gemmation or budding. They rarely figure as pathogenic agents. Typical saccharomycetes, or yeasts fermenting sugar, are occasionally encountered in

the stomach in conditions of dyspepsia, and in the bladders of diabetics. A more atypical yeast has been found fairly frequently on this continent, causing an intractable form of skin disease, and while in most cases the organisms remain localized in the subcutaneous lesions, in some cases they eventually induce lesions also in the deeper tissues. These organisms are found in the tissues in the blastomycetoid form, that is to say, as spherical bodies with hyaline capsules; at times they are found in the act of multiplication by budding. Frequently they are within cells of endothelial type; frequently again these cells, fused, form large giant cells containing numerous organisms. With their toxins they set up a mild inflammation characterized by the accumulation of large endothelial cells with some polymorphonuclear infiltration. The lesion undergoes slow necrosis, and as a consequence the nodules produced under the skin tend to ulcerate and undergo healing; with the slow extension of the process the affected areas show simultaneously the various stages of ulceration, healing, and active infiltration and tumefaction.

Aspergillosis.—Occasionally in the external auditory meatus, and more rarely in the bronchi, we obtain growths of the fungus Aspergillus niger. The hyphæ may penetrate into the tissues, causing considerable irritation and necrosis, which in the lung may be mistaken for tuberculous lesions, but the characteristic mop-like fructifications form only in the presence of air.

Ringworm, Favus, Tinea Tonsurans.—What is true of the aspergillus obtains also for the group of simple moulds which is responsible for a series of highly infective cutaneous affections, involving the hairs and outer layers of the true skin. All the organisms of this series can thrive only when there is abundant oxygen, and as a consequence can induce only superficial lesions. For the very complicated and unsettled question of the number of pathogenic hyphomycetes causing these skin lesions, the student must be referred to the better text-books of dermatology. Here it must suffice to note that these moulds may gain lodgement at some spot, and their hyphæ grow inward between the epithelial squames and down the hair follicles.

In favus, due to the Achorion schönleinii, discovered by Schönlein in 1839, the mycelium at first grows abundantly in the hair sac, insinuating itself between the upper layers of the epithelium, and invading the hair shaft itself, multiplying in the cortical substance of the hair. This leads to disturbance of the nutrition of the hair, which falls out. The papilla atrophies, and new growth becomes impossible. The parasite does not extend into the deeper layers of the skin, but sets up, nevertheless, a low form of inflammation of the corium, and the development of characteristic superficial crusts.

In the various forms of ringworm (Tinea circinata, affecting the skin in general, T. tonsurans of the face and scalp, T. imbricata, tropical ringworm, T. versicolor, etc.) one or more slightly elevated spots of hyperæmia indicate the beginning growth of the mould. From this

central focus the growth extends radially, the parasite dying in the centre, whereby a ring-like zone of hyperæmia indicates the active growing edge of the extension. Several fungi have been isolated, causing different forms of ringworm and favus. As to their relationship—whether they are to be considered varieties or distinct species—dermatologists are still debating.

FIG. 72
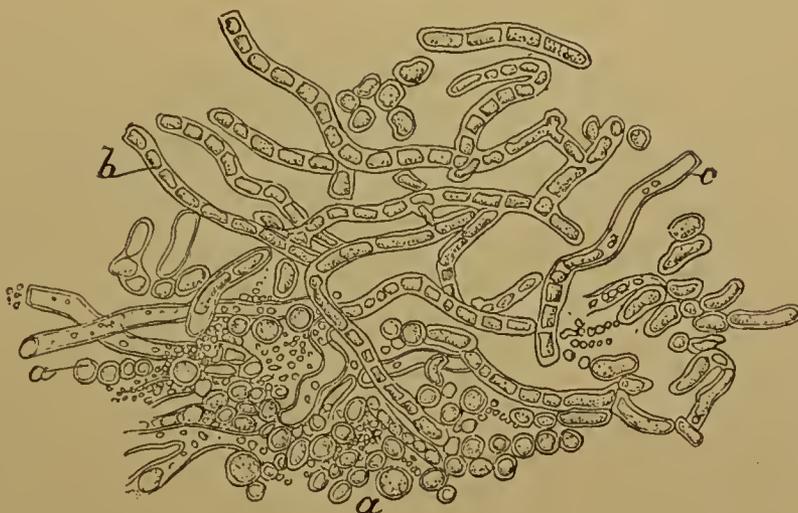
Achorion schönleinii: *a*, spores; *b*, *c*, sporophores. (After Cornil and Ranvier.)

FIG. 73

Sporotrichosis affecting leg. Note the succession of ulcers along the course of the subcutaneous lymphatics. (Dr. W. W. Hamburger.)

Sporotrichosis.—In 1898 Schenck, of Johns Hopkins, called attention to an indolent but very refractory spreading ulcerative condition, often originating from a slight injury, such as a scratch on the finger, this being followed by the development of cutaneous and subcutaneous indurations along the line of the lymphatics, somewhat syphiloid in type, and thus spreading up the limb, but tending to undergo necrosis with the development of crateriform ulcerations, and discharge of a viscid grayish-yellow pus. From this pus a mycelial organism was cultivated, on potato and other media, appearing first as white, woolly colonies which became heaped up, taking on a brownish color. Microscopically there is a felted mycelium bearing numerous spores. The organism is generally found to grow more easily at 22° C. than at blood

temperature. The spores are oval with a pointed extremity, often set singly on stalks. These spores are recognizable in the lesions.

Since 1898 numerous similar cases have been recorded, particularly in North America and in France. The condition has been reported also in Germany, Great Britain, Brazil, etc. It responds readily to the internal and external application of potassium iodide.

FIG. 74
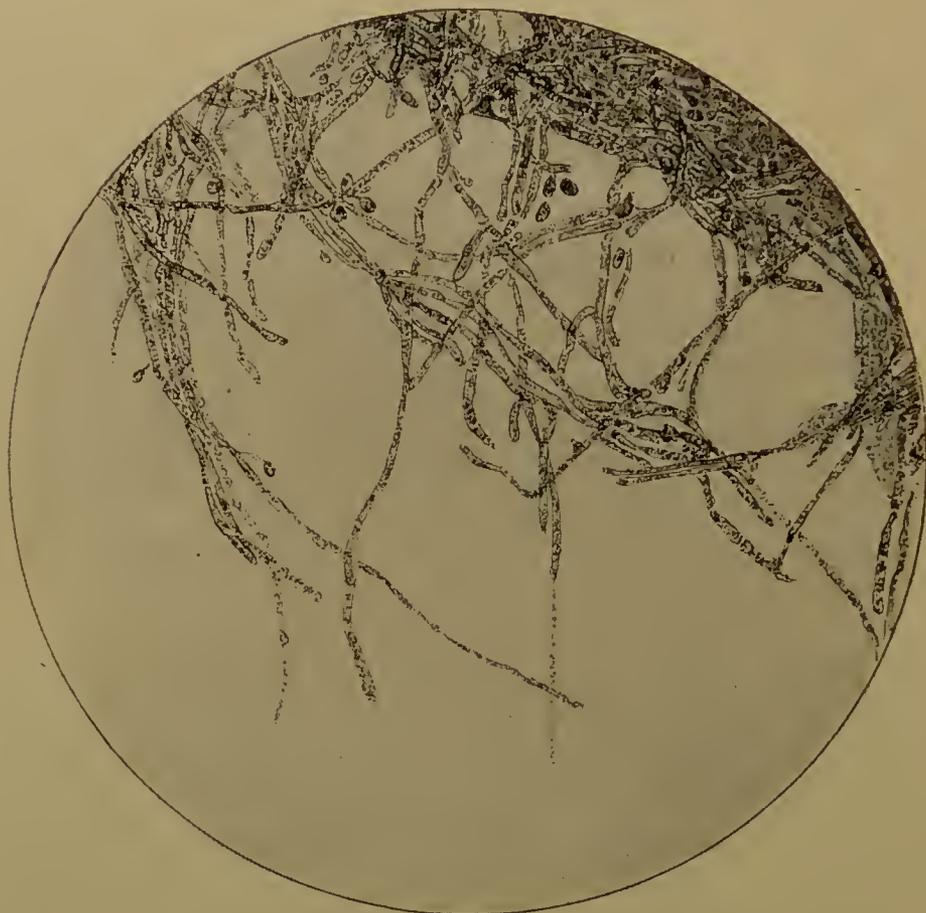
Sporothrix: from a four-day growth in plain peptone broth. Oil immersion. Note the septa in the hyphæ and the early production of spores. (Dr. W. W. Hamburger.)

THE SPIROCHETOSES

Syphilis.—There is no disease in regard to which our views have undergone so material an alteration during the last few years as syphilis, none in which the discovery of the causative agent has been followed by so rapid a revolution in standpoint. It used to be looked upon as allied to tuberculosis in its chronicity, to smallpox in its cutaneous manifestations, and in the long-continued immunity which followed an attack. From the time of its first recognized appearance following the Franco-Italian war of 1495 it has been commonly referred to in many countries as the "great pox" in contradistinction to this latter disease. And the later nervous manifestations such as tabes dorsalis and general paralysis have been regarded not as brought about

by the continued presence and activity of the virus, but as after-effects. Now through the Wassermann test and the demonstration of the spirochete in the later lesions, we regard the disease very differently, and see that the nature of the lesions varies according to the accustomance of the tissues to the virus. The main phases and features of acquired syphilis are briefly as follows:

FIG. 75

From a section of a chancre of the prepuce at the twentieth day from its appearance. The indurating œdema corresponds to a distension and infiltration of the upper layers of the derma, which extends as a zone, x, x, x, about the centre of the chancre at a. The infiltration of the walls of the vessels is also well exhibited, especially at b. (Taylor.)

Infection is nearly always local, through some abrasion, and a fortnight or more may elapse before a local papule is noted at the site of the abrasion; this enlarging in the course of a week or two presents a brawny indurated base, and a low form of ulceration of its centre, without suppuration, but with a thin serous discharge, A scraping from this affords lymphocytes, some polynuclear leucocytes, and abundant spirochetes. In other words, the local proliferation of the spirochetes leads to a congestion and dense infiltration of the part, with eventual proliferation of the surrounding connective-tissue cells, so that this primary sore or chancre heals in the course of a few weeks with the production of a well-marked cicatrix. Even in this primary sore we note the characteristic feature of syphilitic lesions in general, namely, a pronounced perivascular lymphocytosis, with endothelial overgrowth of the intima of the arterioles in the immediate neighborhood, and tendency toward obliteration of the same. In the capillaries this same overgrowth may result in the production of giant cells. Simultaneously with the full development of the chancre the nearest lymph nodes show involvement: they become swollen and indurated. Now follows a period

16

of apparent intermission for several weeks, during which the patient has good health, though toward the end of the period there may be malaise with slight fever, followed by the development, of widespread cutaneous lesions. The simplest interpretation of this latent period is that spirochetes liberated in moderate numbers from the primary sore do not actively multiply in the blood, but, on the contrary, become arrested in the capillaries of various organs. Here the indications are that in the individual of good resisting powers they are in most instances taken up and destroyed by the endothelial cells. In certain regions only at this stage, *e. g.*, the subcutaneous capillaries, do they manage to proliferate until by their very numbers and the accumulation of their toxins they set up a reaction; the time requisite for this secondary or dispersed proliferation constitutes the latent stage above noted.

The rashes are varied in character according to the virulence of the spirochetes and the reactive powers of the individual, from an erythema or diffuse reddening and simple papules up to large bullous vesicular eruptions and multiple ulcerative lesions.

Now there may accompany, or follow, growth of the spirochetes in the internal organs—in the liver, in the vasa vasorum of the aorta and other arteries, the kidneys, the meninges, and periosteum. In general it may be laid down that this diffusive growth of the spirochetes in the florid stage leads like the primary chancre to a localized immunity; the parts which have been the site of spirochetal proliferation are not again involved. And with this if there be not developed a general immunity, there is gained either an increased resisting power on the part of the tissues in general or the spirochetes which survive have lessened virulence. After the termination of this active (so-called secondary) stage the individual usually ceases to be infective, but whether this is because the stage of superficial ulcerative lesions has largely passed, or from attenuation of the virus, is still a matter of debate. This, however, must be emphasized, that the lack of infectivity does not signify the complete destruction of the spirochetes. Unless wholly destroyed by the action of mercury or arsenical compounds these are apt to persist, more especially in certain internal organs; and here they set up scattered, isolated areas of chronic inflammation, over, it may be, a long series of years. The special feature now is the production of "gummas" (or gummata) which may be compared with conglomerate tubercles. At any given focus of continued proliferation of the spirochetes there develops a miliary collection of lymphocytes and proliferated endothelial cells. This undergoes a slow necrotic process differing from the corresponding caseous necrosis in tuberculosis in being preceded by little fatty degeneration. This simpler "gummy" bionecrosis is a characteristic of these later syphilitic lesions. It is associated with the development of new miliary syphilides or syphilitic tubercles immediately around the original focus, which in their turn become surrounded by a ring of new tubercles and undergo necrosis, until in this way a gumma, or mass of dead tissue,

is developed the size of a pea or in some cases, as in the liver, the size of a plum, or even much larger. What is characteristic of all these gummas is the stimulus they afford to fibroblastic proliferation at their periphery; an old gumma becomes surrounded by a zone of fibrosis and as this contracts, the central necrotic matter becomes compressed and finally absorbed, until all that is left may be a stellate cicatrix.

These gummas may slowly develop and undergo regression for many years following infection, and that in various internal organs— liver, lungs, heart muscle (rare), brain, bone, etc. They are not, however, a necessary feature. A man, for example, may die as the result of syphilitic aortitis with aneurysm formation, or from general paralysis of syphilitic origin long years after infection, with no evidence of the present or past existence of gross gummata; nevertheless, in the degenerated media of the aorta or in the brain tissue, spirochetes may be demonstrated, showing that for long years with little or no gross or microscopic or clinical signs of their activity the spirochetes may persist in some tissue or tissues, lying latent for long periods, but liable eventually to take on more active growth.

It is particularly in connection with the nervous

Fig. 76

Section from a gummatous, syphilitic liver, showing at *a* necrotic (gummy) central area; *b*, zone of leukocytes undergoing necrosis; *c c*, zone of abundant small round-celled infiltration; *d d*, outer zone of fibrosis, extending outward between the columns of compressed liver cells at *c*; *f*, bile duct.

system that we encounter these delayed or quaternary syphilitic lesions, either in the form of (1) a chronic productive leptomeningitis, with or without pachymeningitis, (2) locomotor ataxy (tabes dorsalis) with fibrosis and atrophy of the posterior root ganglia, and atrophy and sclerosis of the posterior (sensory) columns of the spinal cord or (3) general paralysis of the insane, in which a similar infiltration, atrophy and fibrosis involves the higher cerebral centres. As indicating the condition of tolerance that is set up it deserves emphasis that these late lesions
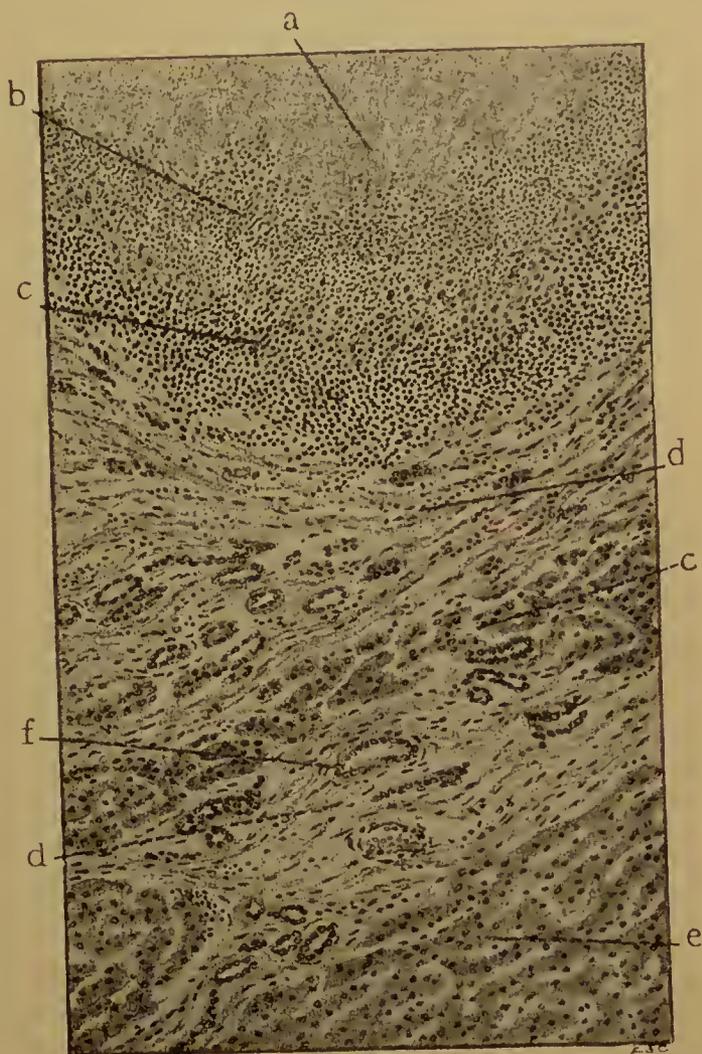
(in which as already stated the spirochetes have been frequently detected) may show themselves twenty and thirty years after the primary infection in cases in which the secondary stage has been very mild, and in which for many years the individual has been in good health, absolutely devoid of any signs or symptoms referable to the disease.

These terminal nerve lesions often bear out strikingly Edinger's "Ersatz" or exhaustion theory, namely, it is in that portion of the nervous system which through constant activity is most liable to exhaustion that the lesions show themselves. Thus general paralysis of the insane with syphilitic lesions in the higher cerebral centres is never found among the lower races, but is common in city dwellers occupying responsible posts, and subject to mental strain. It is the arm centres that are involved in the tabes dorsalis of cabmen; ataxic gait and involvement of the leg centres are seen in men who are much upon their feet.

Congenital Syphilis.—Lastly, reference has to be made to this serious but not infrequent form of the disease.

The old view that syphilis is an hereditary disease, *i. e.*, that the father might convey it to the offspring without the mother becoming infected, with all the surrounding mystery of Colles' law regarding the immunity of the mother to the disease when she suckles her syphilized infant—all this has to be given up now that we understand the nature of the disease. We recognize that the disease is conveyed through the placenta: that the mother is always infected, even if the infection be unrecognized by every clinical means save the Wassermann reaction. The mother of the syphilitic child affords the Wassermann reaction, and that is decisive.

But the mother may become infected before or during pregnancy, and the placenta may become involved at varying periods; thus it happens that the manifestations of the disease at the period of birth vary in their seriousness and extent.

FIG. 77

Spirochetes in liver of congenital syphilis (oil immersion): *a*, spirochete; *b*, nucleus of degenerated liver cells.

The primary lesion or lesions occur thus in the placenta, not in the body of the child. Consequently the newborn child having the spirochetes delivered in the placental blood exhibits the disease in the florid or secondary state, and as the liver first receives the major part of the blood delivered by the umbilical vein, so is this organ peculiarly apt to bear the brunt of the infection. The spirochetes may be present

in the liver in extraordinary numbers, setting up a diffuse inflammation with pronounced swelling of the organ and development of miliary syphilides, followed by diffuse interstitial cirrhosis, if the infant survives the acute stage. Large conglomerate gummata are distinctly rare.

Fig. 78

The raspberry-like nodes of frambœsia. (Todd and Wolbach, Gambia expedition.)

Similar excessive abundance of spirochetes may be determined in the lungs, the adrenals, and other internal organs. Often the abundant proliferation of the microbes leads to death and maceration of the fœtus *in utero,* or to abortion. Often again, the extent of the placental inflammation so interferes with the nutrition of the fœtus that death is to be attributed to this cause.

Should the infant survive this generalized acute syphilis, it may manifest later syphilitic lesions of the skin, especially of the nates and of the mucous membranes, especially of the nose, this often associated with destruction of the cartilage and falling in of the bridge.

Yaws or Frambœsia.—A disease that is not uncommon in certain regions of the Tropics, not only in Central America and the West Indies

but also in Ceylon and southern India, is Yaws, which is characterized by scattered raspberry-like eruptions (hence frambœsia, from the French *framboise*), has by many observers been regarded as a form of syphilis. Castellani, however, has shown that while it is caused by a spirochete, this is recognizably different from the sp. pallida. As with syphilis, the primary lesion is of slow development and occurs on some exposed part, but is not commonly or necessarily the result of sexual intercourse.

The Spirilloses.—We owe to Marchand and Salimbeni the observation that a disease in fowls in Rio de Janiero is due to the multiplication of so-called "spirilla" in the blood, and that infection is conveyed by a tick (*Argas miniatus*). Several years ago, in the seventies, Obermeier discovered a similar organism abundant in the blood of human beings during the febrile attacks of *relapsing fever*. This fever is characterized by a succession of acute febrile attacks, with a temperature of 104° to 106° F., headache and muscular pains, lasting at first for three or four days, succeeded by a quiescent period of seven to nine days with normal

FIG. 79

Ornithodorus moubata, the tick responsible for African "tick" or "relapsing fever."   × 6.
(Dr. J. L. Todd.)

temperature. The successive attacks are of shorter duration. The disease ·is still common in Russia and certain parts of southeastern Europe. During the famine period of the middle of the last century it was common also in Ireland. The associated organism used to be regarded as a spirillum—the Sp. obermeieri—but we now regard it as more nearly related to the spirochetes, and as a matter of fact unlike the bacteria, and like the pathogenic protozoa, Schaudinn found that an insect—the bed bug—is the intermediate host, conveying infection by its bites.

Increased attention has been paid of late years to an almost identical fever in the Congo Free State and in German East Africa. Dutton and Todd have shown that here infection is conveyed by a tick (Ornithodorus moubata) which, occurring in the native houses along the trade routes, has taken on the habits of the bed bug, biting at night, and during the day hiding itself in the crevices of the floor and walls. Just as Theobald Smith and Kilborn showed that in the tick fever of cattle the eggs and subsequent larvæ are infected, so here Dutton and Todd found that the larvæ hatched from the eggs of the infected ornithodorus can infect other beings upon whom they feed.

There are no distinctive pathological lesions so far recognized beyond a moderate swelling of the spleen. In this connection it deserves note that Metchnikoff and other Russian observers find that the disappearance of the spirochetes from the blood at the crisis of each febrile attack is in the main due to an active phagocytosis and destruction of the organisms by the cells of the spleen pulp. Evidently there are resisting forms or a resistant stage, and this destruction of one brood of the spirochetes is followed after an interval by an active growth and proliferation of the same in the blood stream, until they induce a second febrile reaction.

FIG. 80

Tropical sore (East Africa) involving leg and due to spirochetes. (Todd and Wolbach, Gambia expedition.)

Vincent's Angina, Noma, and Tropical Sore.—The resemblance between the spirochetes and the bacteria is emphasized in Vincent's angina, a form of acute necrotic or membranous pharyngitis, usually beginning as a yellowish-white patch on one tonsil simulating the diphtherial membrane, and spreading thence until a large portion of the pharynx and velum palati becomes involved in a superficial necrosis. At times the underlying tissues are also involved and there is deep ulceration. There is an initial fever which usually disappears about the fourth day, with healing and disappearance of the membrane in a week or ten days;

but in some cases the ulcerative condition may continue for several weeks.

Here, as Vincent points out, we deal with the presence of long, slender fusiform bacilli with pointed ends, from 3μ to 10μ in length in association with definite spirochetes, larger and coarser than the Sp. pallida. Both can be stained by Löffler's methylene blue. Attempts at culture have finally been successful (Tunnicliff) and appear to prove without a doubt that the fusiform organisms are one stage in the development of the spirochete.

Similar if not identical organisms are encountered in **Noma**, an acute and rapidly spreading gangrenous condition, developing more particularly in young children who have been weakened by one of the exanthemata. The common site of this fatal gangrene is the cheek, but occasionally it affects the external genitals.

A similar gangrenous condition leading to deep ulceration, but of more chronic nature is not uncommon in Equatorial Africa. In this also fusiform bacilli combined with spirochetes are found in great numbers in the walls of, and discharge from, the ulcers.

There is still some debate as to whether these are true spirochetes. Ruth Tunnicliff in her cultures described the development of endospores within the fusiform bacilli, while the spirals or turns of the "spirochetes" are not uniform, and the movement is at most rotatory, but not progressive. Recently also in certain spirochetes which he has found to be filterable, Wolbach has demonstrated the existence of definite flagella, resembling more those of bacteria than of trypanosomes.

DISEASES CAUSED BY PROTOZOA

These we may classify, as we classified those of bacterial origin, according to the causative organisms. Thus the protozoa are divided into four classes:

I. **Sarcodina**, forms without permanent organs of locomotion, at least in the adults. Locomotion and ingestion of food are by means of pseudopodia. Reproduction may be either by fission, or by sporulation—Example, *Entamœba histolytica*.

II. **Mastigophora** possessing permanent organs of locomotion in the shape of flagella, of which there may be one, two, or more at either anterior or posterior pole, with or without an undulating membrane. There may be both asexual reproduction by spores, and sexual reproduction. Only one of the four subclasses—the Flagellata—is parasitic in man and the higher animals. Examples, *Trypanosoma*, *Herpetomonas*, *Leishmania*, and perhaps the *Spirochetes*.

III. **Sporozoa**, parasitic and often intracellular protozoa, motile in the early stage by pseudopodia, but without organs of locomotion in the adult condition. Reproduction by sporulation. There are several orders so widely different that possibly this can be divided up into several

classes. Among those infecting man may be mentioned: Order **Coccidiidea**—examples, *Coccidium (Eimeria) oviformis*, common in the rabbit, occasionally described in man. Order **Hæmosporidia**—examples, *Plasmodium vivax*, the tertian parasite; *Plasmodium malariæ*, the quartan parasite; *Plasmodium immaculatum*, the parasite of æstivo-autumnal malaria or tropical malaria; *Piroplasma (Babesia) hominis*, which according to Wilson and Chowning is the cause of the "spotted fever" or "tick fever" of the Rocky Mountains.

Among the **Neosporidia**, a sub-class of the sporozoa, are included forms like the *Myxosporidia*, *Microsporidia*, and the *Sarcosporidia* which are parasites among fish, frogs, and invertebrates; the *Sarcosporidia* alone are found in warm-blooded animals, and very rarely in man. It is still a matter of debate as to whether the genus **Cytorrhyctes**, to include Guarnieri's organisms of smallpox and vaccinia, is valid, and whether it is properly to be included among the sporozoa.

IV. **Infusoria**, protozoa of ovoid shape provided with cilia, a vegetative macronucleus, and a generative micronucleus. Example, *Balantidium coli*.

Amœbic Dysentery.—Of the amœbæ which, as every first year student knows, are present in water, some, *e. g.*, the *entamœba coli*, are capable of existing as saprophytes in the lower bowel. In the Philippines and elsewhere identical forms have been cultivated from the drinking water and from the stools. But these cultivable forms have not been found to possess pathogenic properties. The *E. histolytica* found in the intestinal lesions and hepatic abscesses of tropical dysentery,[1] and first recognized as the causative agent of this condition by Kartulis in Egypt, has so far not been cultivated. But although Koch's postulates have not been fulfilled, and the disease reproduced by the exhibition of pure cultures to susceptible animals, the presence of the amœbæ in relationship to the lesions is so striking that no doubts are held as to their etiological value, and it is well established that the introduction of material containing the parasites into the rectum of cats and other animals induces the specific lesions in which—and not elsewhere—the amœbæ are to be found.

In the absence of any knowledge of the mode of growth of the amœbæ outside the bodies of warm blooded animals, we believe that the disease is conveyed by water contaminated with fæcal matter containing the small cystic resistant forms of the amœba. It is held that amœboid, non-cystic forms discharged in the stools are non-pathogenic; that only the cysts resist the action of the gastric juice. Becoming actively amœboid in the lower bowel the amœbæ make their way through the mucosa into the lymph spaces of the submucosa and here set up irritation. The earliest stage recognized thus far is the presence of small

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[1] The tendency today is to regard *E. tetragena* and *E. minuta* which have been described as distinct pathogenic species as varieties of *Entamœba histolytica*. James, of Panama, has shown that *tetragena* is the encysting stage of the organism whose vegatative form is the *E. histolytica*.

FIG. 81
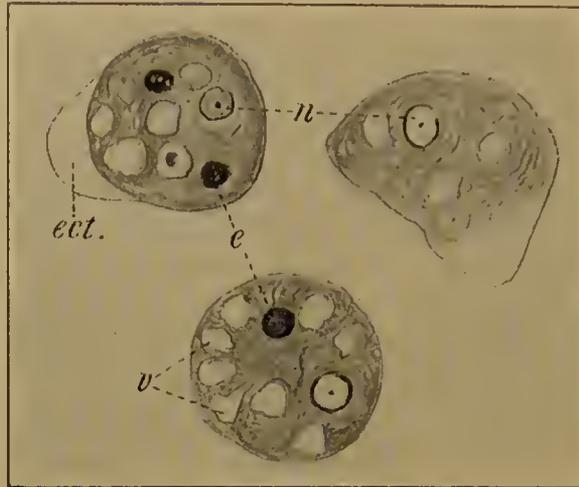
Entamœba histolytica, from lesions in colon. *n*, nucleus (relatively small with nucleolus); *ect.*, clear ectosarc (in the living state, in the warm stage the pseudopodia are formed of this clear ectosarc without granules); *e*, ingested erythrocytes; *v*, vacuoles.

FIG. 82
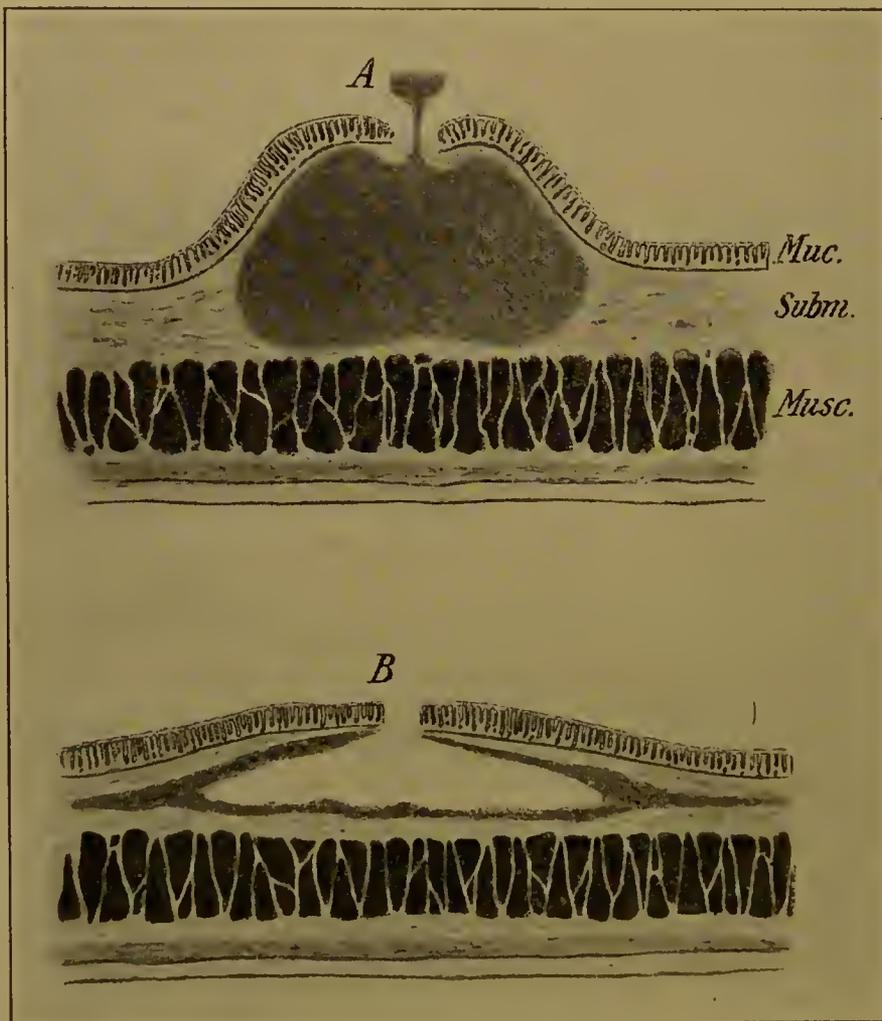
Amœbic colitis. Diagram to illustrate the mode of development of the lesions in the submucosa of the colon. *A*, localized infiltrations of the submucosa with beginning ulceration; *B*, necrosis and discharge of the necrosed material with coincident spread of the infiltration and necrosis in the submucosa.

nodular masses projecting above the level of the gut, with central necrosis of the mucosa and development thus of small ulcers; the nodular shape may be due to the infiltration of the submucosa.

The amœbæ are actively phagocytic, and are frequently to be encountered filled with erythrocytes and cell debris. Added to this they appear to exert a necrotising action upon the cells in their immediate neighborhood. The result is that they set up irritation, and a not very acute form of polynuclear infiltration. This infiltration is followed by necrosis and ulceration of the overlying mucosa.

It is generally taught that the entamœbæ first invade and destroy the mucosa. From the absence of any specimens showing this primary invasion and destruction of the epithelium, we are inclined to the view that this primary necrosis is doubtful.

As the cells undergo necrosis the amœbæ move by the lymph spaces into the immediately surrounding tissue, and in this way there is developed a spreading infiltration and necrosis of the submucosa. In this way, characteristically, the involvement of the submucosa is very much more extensive than that of the mucosa: a relatively small ulcer may represent a large area of undermining; a probe inserted at one ulcer may be passed along tracts of necrosis and softening to emerge at another ulcer at some little distance.

Study of the lesions reveals that the amœbæ may penetrate also into the veins. It is thus that we most satisfactorily explain the not infrequent development of amœbic abscesses in the liver. That these occur more often in the right lobe seems to have its explanation through the observations of Cantlie and Borst, that the blood from the mesenteric veins passes mainly to that lobe. Strictly speaking, in uncomplicated cases these are not true abscesses. When, that is, we deal with lesions set up by the entamœbæ alone, the contents are not true pus, but a thin "anchovy paste" matter containing few leucocytes, composed in the main of dead liver cells and the products of their digestion. Here also the amœbæ exert their necrotising effect. They may be completely wanting in these fluid contents, but are to be obtained in large numbers in scrapings from the shaggy walls of the "abscess." Here they are to be found in the sinusoids between liver cells which have not undergone necrosis. We have obtained them from these regions still actively motile upon the warm stage twenty-four hours after the death of their host. As indicating that they are carried by the blood stream, similar abscesses have been, rarely, described as affecting the brain and kidneys.

For the following synopsis of the differential features of amœbic and bacillary colitis we are indebted to our colleague, Dr. R. H. Malone, and his studies of a collection of some eighty specimens of colitis gathered by Dr. J. G. Willmore at the Egyptian Government Hospital at the foot of Mt. Sinai.

Amœbic Colitis.	Epidemic Bacillary Colitis.
Due to the *Entamœba histolytica.*	Due most often to some strain of *B. dysenteriæ.*
Submucosa primarily involved.	Mucosa primarily involved.
Lesions tend to be most extensive in cecum and ascending colon, next in sigmoid.	Descending colon and rectum apt to be involved.
Bowel dilated and thinned.	Affected bowel most often somewhat narrowed and contracted (in acute cases), with later cicatrizations.
Hyperemia apt to be not so diffuse and extensive.	Diffuse hyperemia and intense congestion a marked feature.
Ulcers not so abundant, may be relatively small and discrete, but communicating, with extensive undermined areas beneath still intact mucosa.	Ulcers of mucosa extensive, with formation of large relatively superficial ulcers often preceded by a superficial membranous necrosis.
Perforation not uncommon; but little adhesive peritonitis.	Perforation less common, but a low form of peritonitis with extensive adhesions.

It deserves note that our collection contains several examples of combination of the two conditions, as also that according to the causative strain so do the lesions of bacillary colitis vary in their region of incidence. Thus Deeks records one variety encountered at Panama especially involving the cæcum.

Trypanosomiasis.—During the last ten years the trypanosomes have attracted much attention, and have been found in the blood of every species of vertebrate. They may set up no obvious disturbance—as in the case of the *T. rotatorium* of the common frog, and the *T. lewisi* in the rat—or on the other hand may lead to extensive mortality as is the case more particularly in the trypanosomiases of domestic animals such as N'gana or tsetse-fly disease affecting horses and cattle in South Africa (due to *T. brucei*), surra among horses and mules in India (*T. evansi*), Dourine or mal de coit in Europe and North America (*T. equiperdum*), "mal de caderas" in South America (*T. equinum*). But one trypanosome disease is known affecting man, and that only in one region, namely, equatorial Africa, due to *T. gambiense;* there it is becoming more and more widespread, extending along the trade routes, and in the last few years the mortality has reached the hundreds of thousands. Trypanosomiasis has thus rapidly attained the rank of one of the deadliest diseases affecting man.

In man, as among the domestic animals, we do not deal with an acute febrile state but with a slowly progressive disorder. With the exception of dourine, which is conveyed from animal to animal by the sexual act, infection in these diseases is carried by blood-sucking insects, and notably by blood-sucking flies; nor are the specific trypanosomes confined to one warm-blooded host. Thus today it is generally accepted that the fly *Glossina palpalis* conveys infection to man from some of the larger wild animals of tropical Africa. After infection there is no immediate disturbance; the trypanosomes live and multiply in the lymph and blood plasma and not, as in malaria, within the erythrocytes. The first recognizable lesion is swelling of the more superficial lymph nodes and, as demonstrated by Greig and Gray, and our colleague, Professor Todd, the earliest diagnosis is obtainable by puncture of the enlarged nodes

FIG. 83
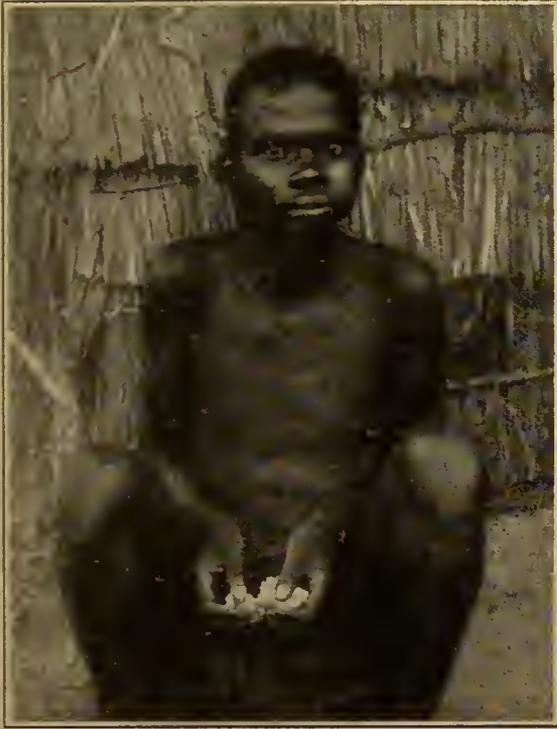
FIG. 84
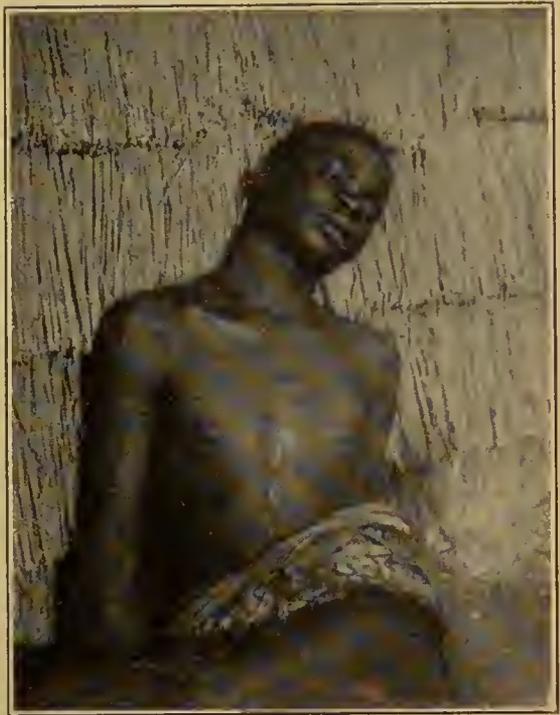
Sleeping sickness. Two photographs taken of a Congo State native with an interval of thirty seconds. In the middle of a meal he dozed off. (Dutton and Todd, Congo expedition.)

FIG. 85
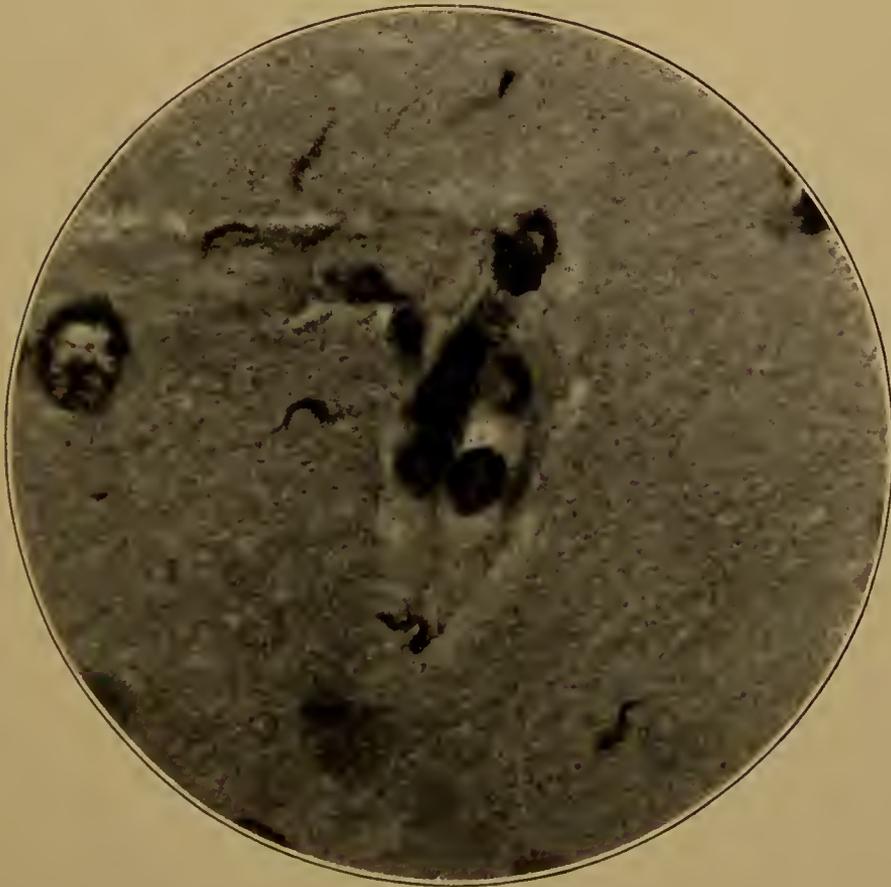
Trypanosomes (T. gambiense, the organism of sleeping sickness) in section of brain of an inoculated monkey. (Professor Wolbach.)

and detection of the parasites in the aspirated lymph. The trypanosomes may be absent from the blood for months at a time. In fact, many months may elapse (in general a year or more) before the characteristic symptoms make their appearance, namely, increasing apathy and disinclination for any effort, even that of eating. With this there is puffiness of the eyelids and change of facial aspect, headache, and liability to fall asleep, or at least to doze. At this stage various muscular tremors are noticeable; later there is wasting of the muscles and emaciation. The increasing lethargy gives place to coma and death.

The irregular temperature often reaching 101° to 102° F. suggests the action of some toxin, but so far the development of toxins by the parasites has not been demonstrated. The main lesion discoverable according to Professor Mott, is a lymphocytic infiltration around the bloodvessels of the brain, most noticeable in the pons, medulla and cerebellum. With this many nerve cells show diminution or alteration in their Nissl bodies, with other signs of degeneration. While in animals infected with trypanosomes the capillaries may be found packed with the parasites, this is not the case in man, in whom as evidenced by the enlarged lymph nodes and the perivascular lymphocytosis, the lymphatic system is more involved. The trypanosomes are present also in the cerebrospinal fluid, and may constantly be gained by lumbar puncture.

Leishmaniasis (Kala-azar and Oriental Sore).—Kala-azar is a very fatal disease which until lately was mistaken for severe malaria or for ankylostomiasis. It has been known for fifty years or so in Assam, spreading slowly from village to village, and characterized by fever, which gives place to great enlargement of the spleen. There are successive attacks of high fever following each other at shorter intervals until a continued febrile state is developed, extending over several months; with progressive anæmia the liver undergoes enlargement. Cutaneous and abdominal dropsy are frequent, as are hemorrhage in various areas—cutaneous (purpura), intestinal, and from the nostrils and gums. Progressive emaciation and weakness with marked cachexia end in death some two years after the first symptom has been noted. Some more acute cases are fatal in the course of a few weeks.

The splenic enlargement is the outstanding feature. What is clearly the same disease occurs endemically and more sporadically in India, China, and other tropical regions, and it was in one of these cases, of so-called "Dum-Dum fever" that Leishman found the bodies with which his name has been associated, Donovan demonstrating their existence in the disease in Assam. These Leishman-Donovan bodies occur in abundance in endothelial cells and leucocytes in the spleen, liver, and bone marrow. Diagnosis is best made by puncture of the liver. Puncture of the spleen while demonstrating them in greater numbers is dangerous on account of the liability to fatal hemorrhage. Seen in the cells they are minute bodies each showing a larger and a smaller chromatin mass, in this not unlike the piroplasmas found in the red corpuscles of Texas fever of cattle. But unlike those organisms

they can be cultivated in the test-tube, and then develop into trypanosome-like or, more accurately, herpetomonas forms, with a distinct flagellum but without an undulating membrane.

FIG. 86
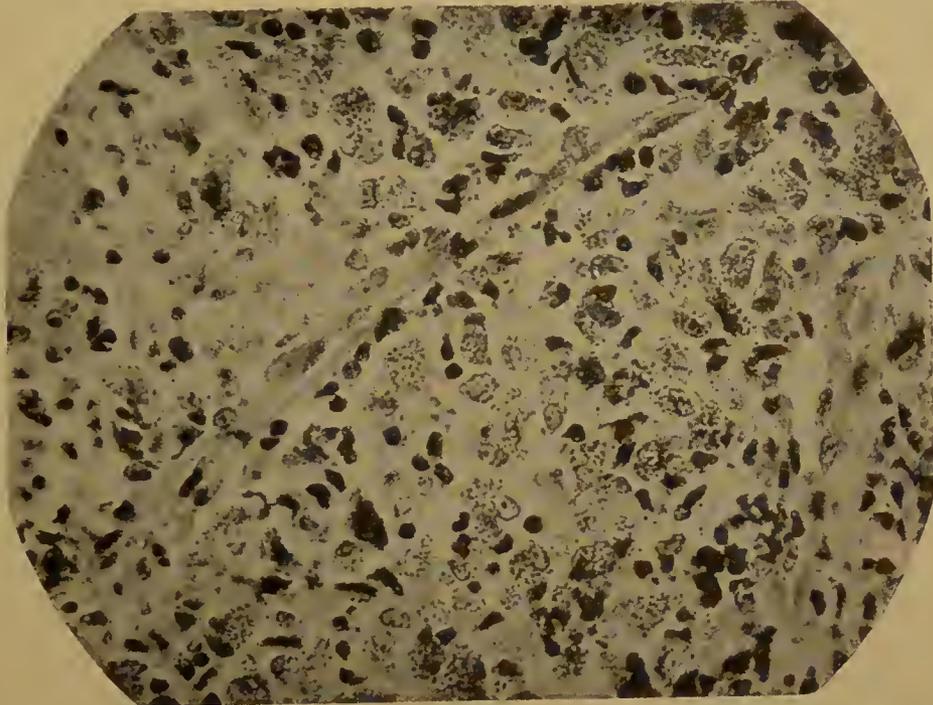
Oriental sore. Section of the lesion showing the infiltrating cells. The granular appearance of the large cells is due to the presence in their cytoplasm of enormous numbers of the causative microorganisms. × 500. (J. Homer Wright.)

FIG. 87
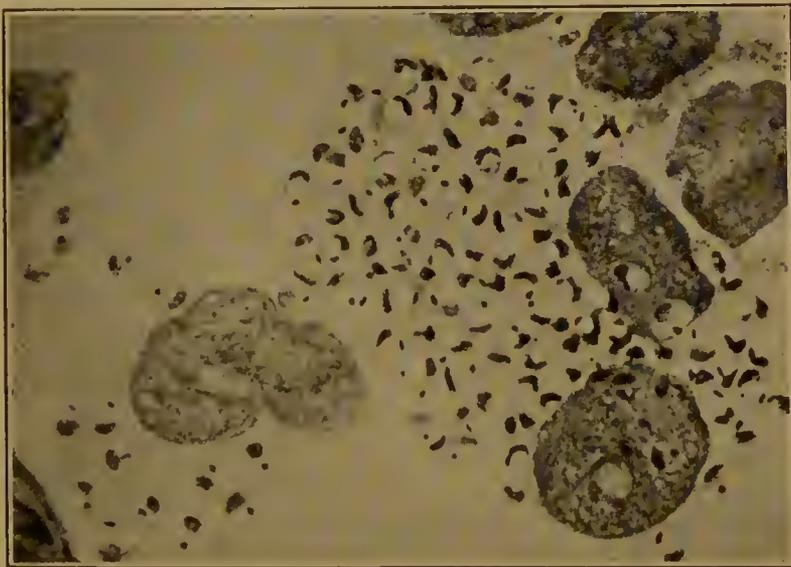
Smear preparation from the lesion of Oriental sore. The ring-like bodies with white central portions and containing a larger and smaller dark mass are the microörganisms. The large, dark masses are nuclei of cells. × 1500. (J. Homer Wright.)

Oriental Sore.—Another tropical disease very widespread is an intractable boil or sore which, according to the regions in which it is common (Asia Minor, India, North Africa, etc.), has received a variety

of names—Aleppo button, Delhi boil, "Clou de Biskra," Kandahar sore, Penjdeh boil, etc. We may speak of it as "Oriental sore." In a case of this condition studied by him, J. H. Wright, of Boston, discovered cell inclusions indistinguishable from the Donovan-Leishman bodies. His observations have received repeated confirmation. It is still undecided whether we deal here with a local cutaneous infection by the organism of kala-azar or with disease set up by another species of Leishmania. The latter view is that generally accepted.

Malaria.—From antiquity different forms of ague have been well recognized: tertian ague with attacks every third day, quartan ague with attacks every fourth day, and irregular forms such as double tertian, double quartan, and yet others. Through Laveran's discovery of the Hæmatozoön malariæ, and the further studies of more particularly the Italian observers Marchiafava, Celli, and Bignami, the meaning of this periodicity has been made clear. We now know that the characteristic ague fits with their rigors and shivering stage, hot stage, and critical perspiration with return to normal temperature, all taking place in the course of a few hours, are intimately related to the maturation of hæmatozoa within the erythrocytes, and the liberation of their spores and—as Bunting has demonstrated—of the hematoidin of the destroyed corpuscles. We know that the difference between tertian and quartan ague depends upon this, that they are due to different species of hæmatozoa, the former having an asexual life cycle of 48 hours, the latter maturing more slowly, so that 72 hours is requisite from the time of the liberation of the spores, through assumption of an amœboid stage, the attachment of the amœbocytes to, and entrance into, an erythrocyte, the growth within the same, until the hæmatozoön undergoes radial segmentation and spore formation, liberates its spores, and the process is ready to begin again. If two infections occur by the same form on successive days, or by different forms on the same day, we may find peculiar periodicity in the chills.

We recognize further the existence of at least one other species that is responsible for the more irregular malignant tertian or æstivo-autumnal form of the disease.

More than this the old view that the disease was of miasmatic origin, due to miasm or evil humors in the air (mal aria) of low-lying or swampy regions, arising with the evening mists, has, thanks to the observations of Ross upon birds, and Bignami upon man, been replaced by the more precise knowledge that infection is through the bites of anopheline mosquitoes; while W. G. Macallum by his studies upon an allied parasite in Canadian crows supplied the necessary link in our investigations of the life history of the hæmatozoön. While in the human body the parasite multiplies by a succession of asexual sporulating cycles in the blood, outside the body, namely, in the stomach of the mosquito, certain of the free hæmatozoa develop into male elements or gametocytes, and give off motile processes or filaments—the homologues of spermatozoa —which, entering into conjugation with female gametocytes, form

zygotes or fertilized individuals which, penetrating the mucosa of the stomach, grow and give origin to innumerable schizonts and these becoming free find their way into the salivary glands and so to the proboscis of the mosquito, which in its turn introduces them into the tissues and blood of a new human host. A study, therefore, of the mosquito (Anopheles), of its nocturnal habits, of the way it lays its eggs (on stagnant or slow flowing water), of its development in water, the limited range of flight of the adult insect—all these matters explain to us the mode and means of infection, and what is more have indicated the proper means of prevention.

Fig. 88
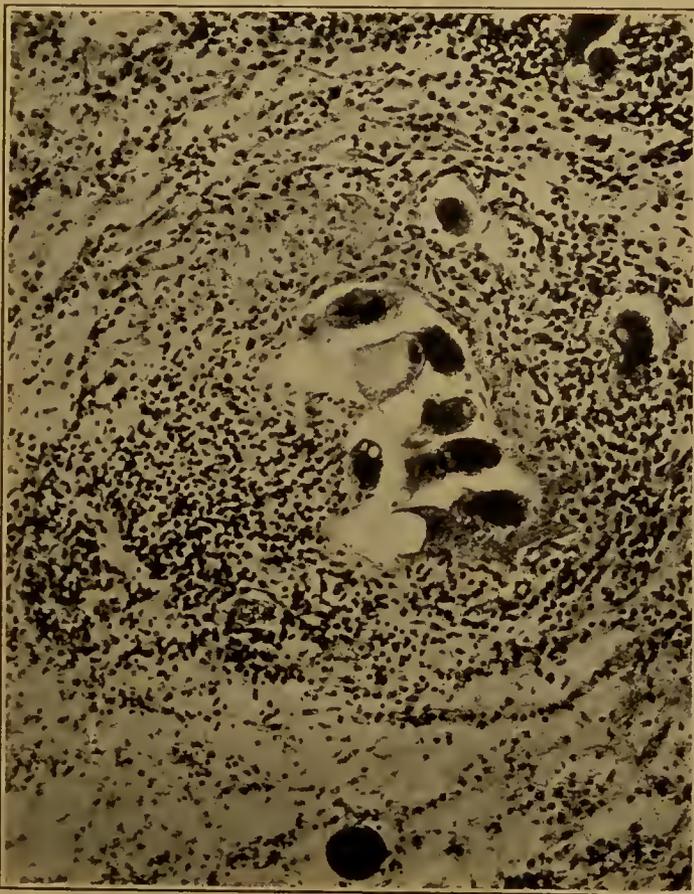
Section of the large intestine of a man dead from balantidial dysentery: an early stage of a balantidial abscess in the submucosa. Note the small cavity filled with balantidia and the infiltration of the surrounding tissue with mononuclear cells. (From a photograph by Charles Martin. E. L. Walker, *Philippine Journal of Science*, vol. viii.)

This much, rapidly, regarding the etiology of malaria leads to the lesions characteristic of the disease. The hæmatozoön as already stated, lives within the red blood corpuscles and brings about the destruction of the same. Thus it is in connection with the vascular system, the blood forming organs, and those which deal with effete corpuscles, that the main lesions are to be encountered. The invasion and destruction of a series of erythrocytes every 48 or 72 hours leads to definite anemia; the liberation of the modified pigment into the blood serum and so into

the lymph, tends toward a distinct grade of pigmentation in the skin, or characteristic sallowness quite distinct from the pallor of an uncomplicated anemia. But more particularly in the spleen, whose function it is to filter dying corpuscles and corpuscular debris from out of the circulating blood, do we find evidence of increased function, shown by increased rusty pigmentation, and at times where the disease has been of long continuance by distinct enlargement and chronic fibrosis ("ague cake"). In the earlier stages the enlargement is little noticeable, and instead of being firm, the organ may be soft and almost pulpy. With this increased action of the spleen upon the erthyrocytes we find as in Banti's disease (which also is characterized by increased splenic function and discharge of the products of erthrocytic destruction into the portal vein) that eventually a certain grade of fibrosis is set up in the liver.

Frequently a noticeable feature is the taking up of the pigment masses from the destroyed corpuscles by the vascular endothelium in various organs. In this way pigmentation may be encountered along the capillaries of the brain, kidneys, etc. At other times the capillaries become absolutely blocked by pigment masses. It is doubtful whether the pigment alone is the cause of the blockage. The indications are that the spores of the parasite at times are liable to be agglutinated and to remain adherent, and that it is these larger masses with their attached pigment which act as capillary emboli, and arresting the circulation in minute areas lead to fibrotic and functional disturbances.

FIG. 89

Balantidium coli showing nucleus (on the right), vacuoles (on the left), peristoma (placed uppermost), and a mass of food ingested (toward the lower end of the figure). (After Leuchart, from Braun.)

Balantidiasis.— Within the last few years several studies have been made upon a condition resembling amœbic colitis (or amœbiasis) in several of its features, in which the pathogenic agent is not an entamœba, but a ciliate infusorian, the Balantidium coli. The condition occurs more particularly in tropical and subtropical regions: thus several cases have been reported from the Philippines since their occupation by the United States. It is interesting to note that the Balantidium coli is common in the intestinal canal of hogs in many parts of the world; there is still discussion as to whether the organism is one and the same in the two species. In man, with one exception, the ulcers have been found confined to the colon; they are not characteristic; the parasites besides being found in the submucosa have been detected in the mesocolic lymph nodes; liver abscesses are almost unknown.

CHAPTER V

THE REGRESSIVE TISSUE CHANGES

GENERAL CONSIDERATION OF TISSUE CHANGES

HAVING considered morbid changes from the standpoint of the irritant, it becomes necessary to view them with reference to the alterations produced in the tissues. Looking at the individual cell, we see that the factors determining its health or normality are: (1) the nutrition of the cell, and (2) its functioning or activity, and these two are intimately dependent upon one another. The process of nutrition is an active one; only that food which is of the proper quality tends to be assimilated, and assimilation is needful before the nutrition can occur. Function is necessary as well; the more active the function, within limits, the more active the absorption of new material, and the less the function the less the demand for assimilation. The two factors, food and function, are seen to be inextricably bound to one another.

Although the subject has been previously discussed, there are certain general principles to be remembered, which are here recapitulated; that inadequate nutrition or lack of exercise of function may lead to inanition and shrinkage until arrest of function or even death ensues; that excessive activity may so rapidly use up the cell that assimilation cannot keep pace and death may ensue; that so perfect a balance may be reached between assimilation and disintegration by activity that the cell may for a long time remain in health, unaltered; that stimulation and activity even above the normal, if accompanied by adequate

nutrition may lead to growth, and equilibrium be once more reached, this time on a higher level, just as a mercantile business increases the scale on which it works without loss of efficiency; that there is a relation between cell mass and cell surface, and nuclear mass and nuclear surface, so that increase becomes self-inhibitory unless cellular and nuclear proliferation occur; that growth and function are opposed processes, which can occur simultaneously only within narrow limits; that specialization of the cell for and through the performance of function limits growth and proliferative capacity; that the highly developed cell does

Fig. 90

Artificial cultivation of tissue. Sarcomatous tissue from a rat, which shows the characteristic radial growth assumed in the cultures. Two cells are seen which are in a state of mitosis. (Hanes and Lambert.)

not proliferate, and that the active vegetative cells of the organism are those that have never been highly differentiated, or if they have been differentiated, have reverted to the undifferentiated type.

If we pass from physiological to pathological growth or overgrowth, arises at once the question as to the cause of that growth. Some think that such growth originates wholly in the cell, and that an effective stimulus to growth outside the cell does not exist, a point of view which we cannot share. It seems likely that growth depends somewhat upon tension of surrounding cells, or better that growth is restrained by the effect of surrounding cells, but it appears that this cannot be all, for, more powerful than the restraining effect of the surrounding

cells, an external stimulus may arise that is powerful enough to more than neutralize these influences.

We find that there is a considerable number of circumstances or combinations of circumstances that may lead, on the one hand, to cell overgrowth, or, on the other, to cell shrinkage and degeneration.

Thus overgrowth may arise from:

1. Normal activity with increased nutrition.
2. Increased activity with increased nutrition.
3. Reduction in the external forces inhibiting cell growth, *i. e.*, diminished tissue tension.

These changes in tissue we call **progressive.**

Shrinkage and degeneration may arise from:

1. Normal activity with reduced nutrition.
2. Normal activity with perverted nutrition, the food material being of the wrong kind.
3. Increased stimulation or overstimulation and activity with relatively insufficient nutrition.
4. Arrest of function.
5. Increase in the external forces, arresting growth.

These changes are **regressive.**

But these classes do not cover all cases. It will be remembered that there is a group of cases in which the changes are not so evident in the protoplasm as in the paraplasm (a single example is the so-called fatty degeneration), and since these changes are either due to or lead to regressive changes in the protoplasm, they are included among the regressive changes. On the other hand, there is the important series of the neoplasms in which one cannot state what is the primary cause of the excessive overgrowth; these are naturally included among the progressive changes.

NORMAL HISTOLYSIS AND CYTOLYSIS

For a proper understanding of the regressive tissue changes, it is necessary to consider how the tissues naturally decay, for however rarely we pay attention to this phenomenon, it is going on constantly. Tissues and organs in the embryo, representing ancestral structures, appear and disappear. The thymus reaches its maximum during the first three years of life and undergoes absorption, although it may remain large and distinct until adult age; nevertheless, histological examination shows that even in childhood its lymphoid elements become replaced largely by fat cells; the lymph nodes, at their largest in youth, become smaller; the milk-teeth disappear before the inroad of the permanent set; after pregnancy the uterine tissue undergoes involution, that is, the cells which were hypertrophied, atrophy; the ovaries atrophy at the menopause. Red-blood corpuscles and leucocytes have a life of but a few weeks; they disintegrate and are eaten up by other cells;

even so solid a structure as bone is undergoing constant change. All this is but the analysis of the popular saying that the tissues are renewed every seven years. The particular definite length of time has no foundation, but the principle is true.

The destruction of cells in the ordinary wear and tear of tissues is doubtless a complex process, the result being due to changes in the cell itself, as well as to forces acting outside the moribund cell. Only rarely are we in a position to recognize the signs of approaching cell death by any special histological change. Thus Metchnikoff has called attention to the presence of phagocytic cells around moribund ganglion cells in the brain. But we can tell sometimes that cells are growing old; in senile atrophy, for instance, the cells grow smaller and often lose finer details of structure, such as the transverse striations of muscle fibres. A cell in this state of senility is not so capable as it once was of carrying out its functional duties, and substances which it absorbs are not properly or completely converted and tend to be stored up; the products of its own cell disintegration, if not soluble, in a similar way tend to be stored up, so that by the presence of paraplasmic material in the cell we may recognize its senility, either natural or premature. An excellent example of this is seen in the so-called brown atrophy of the heart-muscle cell, in which the cell is seen to be smaller than normal and to have at each pole of the nucleus a deposit of fine reddish-brown granules, which are thought to be the final insoluble product of the breaking down of myohemoglobin. (See Plate VII, Fig. 1.)

Equally good as an illustration is the change wrought in the muscle of the uterus after parturition. During pregnancy the muscle fibres have undergone immense hypertrophy, and during the first week after delivery they shrink in a degree no less remarkable; from being on an average 208μ long, they become reduced to 24μ (Sänger). In addition, they look more cloudy, and sometimes show refractile globules of fat. This is fatty degeneration, and a simultaneous fatty infiltration is visible between the deeper muscle cells, this fat disappearing with considerable rapidity. We have in this example cloudy and fatty degeneration and fatty infiltration all occurring in a process which we regard as normal.

The factors which are most potent in determining the state of a cell are **nutrition** and the **performance of function**; if nutrition be good and there be loss of function, atrophy will supervene from disuse; if there be excessive function with normal nutrition, there will also be atrophy.

Causes of Atrophy.—Briefly, we find various orders of atrophy: (1) disuse atrophy; (2) atrophy due to excessive function; and (3) atrophy due to lack of nourishment.

1. **Disuse Atrophy.**—The enforced rest of muscular tissue brings about true atrophy, that is, not necessarily a reduction in the numbers of the cells but a reduction in the size of the individual cell; this will result from the immobilization of a limb by mechanical means, or if the nerve be severed. Disuse atrophy is very well shown in the nervous

system, in which it was for long thought that when an axone was severed, a degeneration only in the distal severed part occurred; but there is more than this, for a disuse change occurs even in the nerve cell body, and this is especially so in areas where, in health, there is a constant succession of stimuli reaching the cell; in the absence of these stimuli there is atrophy.

FIG. 91

Atrophy of bones of leg from disuse, in a patient who was insane. Note the extreme slenderness of the shaft, in proportion to the length. (McGill Pathological Museum.)

2. **Atrophy from Overwork.**—Overwork, carried beyond a given limit, tends to induce cell-exhaustion, if continued, to produce cell atrophy. It is difficult to bring forward clear examples, but we would suggest that certain of the professional palsies belong to this category.

3. **Atrophy from Malnutrition.**—The alteration of the body from general starvation is a case in point, as well as the atrophy of special areas whose arterial supply is pressed upon and lessened; even the atrophy caused by pressure is another example of the same, the most

dense-tissues, like bone, undergoing atrophy when subjected to constant pressure even by a fluid mass.

Senile Atrophy.—A closely allied form is senile atrophy—the natural wearing out of the tissues; but there is another factor concerned, for in some people the process begins at an earlier period than in others. Some tissues, too, grow old more quickly than others, and as a general rule the first to atrophy are those that become functionless during the natural life; next to these come the lymphoid structures—lymph nodes, Malpighian bodies of the spleen, and the red bone-marrow—which undergo great diminution; next to these come "store-house" tissues, such as the fatty tissue. Nervous tissue, ordinarily, shows atrophy least of all.

When fatty tissue atrophies, the fat gradually melts away until the cell once more becomes indistinguishable from surrounding connective-tissue cells, but sometimes instead of this the place of the fat is taken by a serous fluid, so that a large mass of fatty tissue so altered appears translucent and jelly-like. This so-called **serous atrophy of fat** is not definitely known to be a purely senile change, but may be so regarded. When the cells of the active tissues atrophy, we have first diminution in size, true atrophy, then in more extreme stages a diminution in number (**hypoplasia**), and along with this the deposit of pigment, especially in those cells that normally contain pigment. This pigmentation occurs in brown atrophy of the heart, as we have already indicated, and it happens similarly to a marked degree in the liver.

In bone the process of atrophy is a rarefaction whereby there is an actual loss of bony substance, the individual bones become lighter, and there is an increased liability to fracture. The loss of substance is largely central, the medullary cavity and the Haversian canals being increased in size, and the trabeculæ and lamellæ thinned; the red cellular marrow becomes replaced by fat, which again may undergo the before-mentioned serous change.

The characteristic changes in the senile skin are due not so much to any epidermal changes as to a loss of subcutaneous fat and fluid, accompanied, of course, by actual tissue shrinkage; the elastic tissue of the dermis is also altered, becoming less resilient. This elastic tissue change becomes very important in the senile degenerations that occur in the arteries and the lungs. In the arteries, as the walls lose their resilience, the arterial tube dilates and is unable to recover itself, remaining permanently expanded. At this stage, when the expansion is permanent, we may find so diffuse an enlargement as to constitute a **fusiform aneurysm**, or if localized, a **saccular aneurysm**, although these rarely if ever arise from senility alone. In either case, the wall is found to be thinned and atrophied, and some layers, especially in the muscle, may disappear. The increased caliber of the vessels causes a slowing of the blood stream and the consequences of the same in the tissues supplied. But along with this atrophy of the wall proper, we have a series of important compensatory changes; as the arterial wall gives way, there is a connective-

tissue overgrowth in the intima, as a result of which the lumen is restored; this process is **arteriosclerosis.** Although the compensation may be in bulk equivalent to the tissue lost, and may ultimately come to contain elastic fibrils, yet the wall has lost in elasticity, so that the pulse waves are conveyed with greater force, or at least with less modification, into the arterioles, which in turn undergo a similar change to the detriment of the tissues supplied. A like loss of elasticity in the tissue of the lung gives origin to **emphysema**—dilatation of the air sacs; with the lung tissue in this relatively non-elastic state, suddenly increased intrapulmonary pressure, such as occurs the moment before a cough "explodes," tends to rupture the weaker interalveolar walls so that several alveoli are thrown into one, and the distension thus produced, which ordinarily is rectified by the elasticity of the lung tissue, remains permanently. The increased intrapulmonary pressure which brings about this distension bears upon the capillary walls, and a greater amount of work than normal is thrown upon the right ventricle. Coincident with the distension of the alveoli there is a deposit of connective tissue around the arteries and bronchi which doubtless owes its origin to bronchitis.

Throughout the tissues of the body, with the exception of the nervous system, there is everywhere to be seen, along with senile atrophy of the specific tissues, this relative increase of the lower, supportive tissues. This is partly relative, that is, as the other tissues abate, the fibrous tissue comes into greater prominence; but more than this, there is actual increase, a replacement fibrosis; and this is more pronounced in the perivascular (periarterial) regions than elsewhere. Such a *progressive* change is not to be regarded as an essential part of senile *regression*, but rather as a concomitant occurrence. The nervous system was stated above to be an exception; here, it is true, there is periarterial increase, but there is relatively little or no gliosis; the place of lost substance is filled not by tissue, but by fluid, a **hydrops ex vacuo**, which is the reason for the **œdema of the pia** so often observed at autopsy in those far advanced in life.

Abiotrophy.—A condition allied to senile atrophy, called by Gowers abiotrophy, requires mention. There are certain familial paraplegias, such as Thomsen's disease and the so-called parasyphilitic maladies that lack explanation, as well as paralyses developing in the most exercised limbs. Certain cells and systems of cells degenerate, and ultimately become disorganized, the rest of the system remaining unchanged, and this often in a way that suggests that the trouble is connected with heredity. The conception of abiotrophy is that these cells begin life with less resistance, with less potential energy than others, so that a stress that is no greater than normal exhausts them, even although this stress be no other than the usual work that is demanded of such cells. An experiment that exemplifies such a general abiotrophy is to expose frog spermatozoa to the x-rays; the ova are fertilized, but the larvæ, after a few days' growth, expire prematurely, cell-exhaustion

having supervened. This conception of abiotrophy is to be distinguished from Edinger's "Ersatztheorie" or exhaustion theory, employed to explain the incidence of certain paretic conditions in tabes, etc. According to this theory the syphilitic or other toxin is apt to lead to the premature wearing out of those cells which are most constantly exercised.

Reversionary Metamorphosis; Kataplasia.—While studying atrophic changes, it is necessary to mention a regressive process that may sometimes be found accompanying them. In this, highly organized cells are seen to change to a less specialized state, to become more embryonic, a condition of affairs that has been well observed in muscle fibres; just as the sarcoblast by slow transition becomes the muscle cell in a progressive way, so the muscle cell may become the sarcoblast in a regressive

Fig. 92

Reversionary atrophy from a case of fibrosis of the lung. The alveoli shrunken by the growth of the surrounding connective tissue have become lined by a cubical epithelium, resembling that seen in the lung of the fœtus.

way. The most commonly seen example of the process is in the liver, in which the bile-duct cell and the liver cells have a common origin, and a tubular arrangement of cells is the earliest grouping that is seen; in the developing liver there is a time during which the liver cell and the bile-duct cell are not to be recognized one from the other. When, as happens in cirrhosis of the liver, the liver cells begin to atrophy, the transition from liver cells to bile-duct cells becomes gradual, and cells or groups of cells isolated by the connective tissue at the edge of a lobule are of an intermediate type, smaller than liver cells, and larger than bile-duct cells, in fact, a reversion to the period in which the two were not differentiated. These groups of cells are often called proliferated bile ducts, but they are not true bile ducts by reason of the imperfect arrangement of the cells. In this very instance, it must be kept in mind that the process just described may well be associated with the opposite process, that of a compensatory hypertrophy, the still per-

sistent bile ducts, as the lower type, proliferating to supply the lack of liver cells, and it may be quite impossible to say whether an individual intermediate cell is in progression or regression.

Another oft-seen example is the assumption of a cubical shape by the cells lining lung alveoli in compression of the lung or interstitial fibrosis, which is a reversion to the type of cell seen in this situation before pulmonary respiration began; similarly in the kidney, in nephritis, the epithelium of tubules and of glomeruli may be seen to take on the embryonic cuboidal shape.

THE DEGENERATIONS AND INFILTRATIONS

Even in simple atrophy we are dealing with more than a mere progressive reduction in the volume of the cell-constituents, for we have also certain changes in the nature of the cytoplasm itself. This very heaping-up of what we term by-products must tell deleteriously upon the cell and its activities. It was thought, but now seems less certain, that we could distinguish two processes, which might accompany each other, one the change wrought in the cytoplasm itself leading to the appearance in the cell of such changed products, and the other characterized by the appearance in the cytoplasm of substances obtained from outside the cell, and, it may be, imperfectly handled by the cell. It was thought that the former were degenerations proper and the latter infiltrations, but further study shows that it is becoming increasingly difficult to separate the two, that, in fact, they are too closely related to permit of being considered apart. Especially does it seem to be that true infiltration, by itself, is a rare occurrence. Cells, it is true, become infiltrated with or contain the substances in question, such as fat or glycogen, but it is doubtful if this is sequent to a process of absorption of the fat or glycogen as such; it is more likely that these materials are the result of synthetic processes, the activities of the cytoplasm being responsible for their appearance. For example, fat as such is not to be detected in the blood, for it is to a great extent saponified before its absorption by the intestinal mucosa, where it is converted into a soluble compound. This the liver absorbs from the blood, and reconverts, by its ferment activity, into fat. When globules of fat appear in the diseased cell, it is not likely that these arise from the breaking down of the protein of the cytoplasm, but rather they appear, perhaps in excess, as a sign of the lack of competency to deal with them on the part of the cytoplasm. Whatever be the source of these paraplasmic substances, degeneration and infiltration are so closely linked that they may well be considered together; in many cases, in fact, they are inseparable. It does not, however, follow that each instance of degeneration is accompanied by evidence of infiltration nor is the presence of infiltration proof that a visible degeneration is also to be found.

Cloudy Swelling.—Perhaps the most common morbid change seen at autopsy is that of cloudy swelling or albuminous degeneration, in which the cut surface of the organ has a dulled appearance, as if it had been momentarily dipped in boiling water. With this there is a certain amount of swelling which, in the kidney, causes the cortex to rise above the level of the medulla and makes the cut edge evert. The individual cells have lost transparency, and an unstained section will show, by transmitted light, the cells or groups of cells that are cloudily swollen as shaded with gray, contrasting with the clear white of normal tissues. On close inspection, the nuclei look as if obscured by the deposit of a finely granular material in the cytoplasm, and they stain less intensely than usual. Weak acid or weak alkali clears up this cloudiness, apparently by dissolving out the precipitated proteid or albuminous material.

Fig. 93
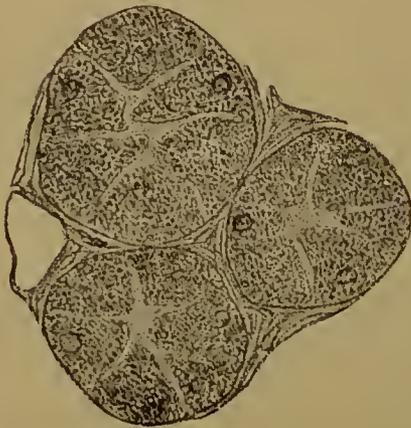
Fig. 94

Cloudy swelling of cells of convoluted tubules of kidney. × 400. (Ribbert.)
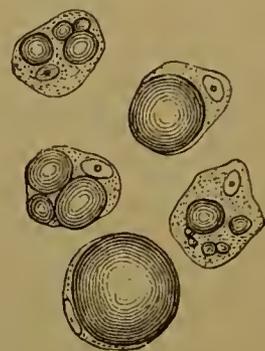
Liver cells in various stages of fatty accumulation. × 300. (Rindfleisch.)

Cloudy swelling is found in the cell under many different conditions, chief of which are acute infections and high fevers; it is seen also in various intoxications, after chemical poisons, in burns, and even in starvation; the granular material which appears is evidently a product of altered cytoplasm, and seems like the granular material ordinarily described as **Altmann's granules**, but with this distinction, that it seems aggregated into larger masses, and there is none of the regular linear arrangement seen in the normal. It is not possible to say definitely what this material is; according to Martin Fischer, it is to be regarded as the result of conversion of certain colloids of the cytoplasm from the soluble into the solid or "gel" state. It is evidently either material disintegrated from the cytoplasm or material absorbed and not completely "handled" by the cell; or finally, it may be both. The increase in size is partly due to the increase in these paraplasmic materials, but mainly to a hydropic condition and increase in the watery constituents.

Cloudy swelling is not to be confounded with granular degeneration, which is a disintegrated state of protoplasm, and a precursor of cell death; the granules or droplets, at least the larger of them, are due to liquefactive necrosis. The process of cloudy swelling thus seems to be

the expression of overstimulation of the cell, with disordered metabolism and the heaping up of paraplasmic matter of an albuminous nature; apparently it is not a necessary cause of cell death, is frequently recovered from, and yet is probably the earliest stage in what may be the progressive deterioration of the sick cell.

INTRACELLULAR FAT ACCUMULATIONS

As was said above, two states are to be considered—fatty infiltration and fatty degeneration. Pronounced examples of each are readily distinguishable, but in many cases the two seem to be blended.

"Fatty Infiltration."—Neutral fat is a constituent of most of the tissues of the body, but in a state unrecognizable by ordinary micro-chemical means. The kidney tissue may be demonstrated to possess fat to the extent of 23 per cent. of its solids, yet may by staining reactions show no trace. On the other hand, certain regions such as the subcutaneous connective tissue, the omentum, the appendices epiploicæ, the cardiac grooves, and the area around the kidney, normally contain fat in large amount, the cells being distended with it. This is not fatty infiltration; that term should be confined to describing the presence of fat cells elsewhere, especially in the interstices of tissues, which are not normally thus laden. True fatty infiltration may thus occur between the cardiac muscle fibres, in skeletal muscles, or in an organ like the pancreas. The liver cells, too, may become the seat of a notable fat deposit, for example, during pregnancy, and this is perfectly properly spoken of as fatty infiltration; it may be very extreme in such states as chronic alcoholism, where four-fifths of the total solids and 41 per cent. of the cell substance (including water) in a given case have proved to be fat. It is to be remembered that in *all parts of the body* fatty infiltration affects the connective tissue; in the *liver*, the connective-tissue cells are not involved, but the liver cells proper.

Fatty infiltration may thus arise from a number of causes:

1. **Physiological.**—There may be a heaping up of fat in the liver during pregnancy and lactation apparently as a preparation for the latter.

2. **Overnutrition.**—The "foie gras" of the overfed Strassburg goose is a familiar example of this.

3. **Substitution.**—Fatty infiltration and not cirrhosis, as popularly supposed, is the most common affection of the liver in alcoholics, notwithstanding the fact that the confirmed alcoholic is not a heavy eater; alcohol, being a foodstuff capable of easy oxidation, probably replaces the fats, and these, not being oxidized, remain and accumulate in the liver cells.

4. **Diminished Oxidation.**—(*a*) *Congenital.*—There are some people naturally obese just as there are others naturally spare. The former perform their metabolism slowly, and the defective oxidation of their

fatty acids leads to a gradual accumulation of neutral fats in the cells. Thyroid extract lessens obesity in such people, probably by reason of its accelerating the oxidative processes.

(b) *Through Disease.*—Fatty infiltration, of the liver often, and of the other tissues sometimes, occurs in those ill of a wasting disease (noted in tuberculous cattle), because lowered vitality and low functional activity of the tissues mean lessened burning-up of the fats taken as food, while fat from the subcutaneous and other tissues may be transposed to the liver.

Fig. 95
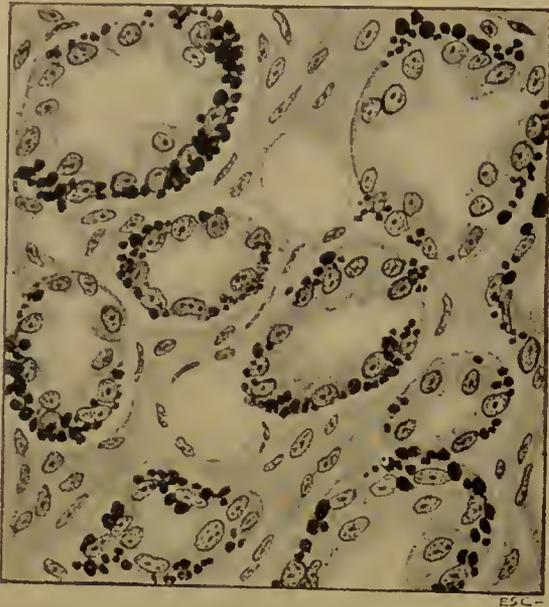
Section showing fatty degeneration of the epithelium of the renal tubules. The fine fatty globules are accumulated in the main toward the outer aspect of the cells, close to the basement membrane.

Fig. 96

Fatty degeneration of liver cells: *b*, fresh cells, cloudy and granular, nuclei not clear; *a*, the fine, fatty globules seen more clearly after treatment with acetic acid. (Ribbert.)

Fig. 97
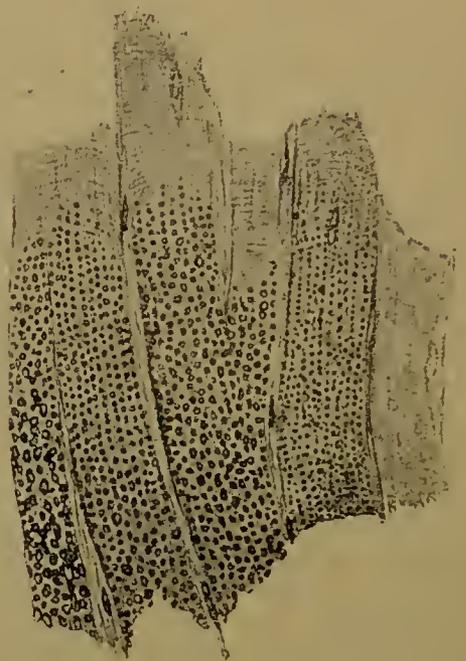
Fatty degeneration of heart-muscle fibres, showing different grades of involvement of the individual fibres; fresh specimen. (Ribbert.)

"Fatty Degeneration."—In the cases of fatty degeneration that appear to be truly such, there is primarily a cell degeneration, the fat being deposited as a result of depressed cell activities. The nuclei may stain poorly, and in the cytoplasm are minute, dust-like fatty bodies which, stained with Sudan III or Scharlach R, give to the cell a diffuse orange-red color, the high power showing that this is due to abundant minute fatty dots. The tissues so affected are: (1) those liable to cloudy swelling (gland cells, especially of the liver and kidney (see Plate VIII, Fig. 1), and muscle fibres, especially of the heart (see Plate VII, Fig. 2); (2) endothelial cells of bloodvessels, and (3) certain cells undergoing normal regressive changes (cells of the sebaceous glands, of the mammary gland).

PLATE VII

FIG. 1

Brown Atrophy.

Brown atrophy of heart, from section stained by hematoxylin, to show the accumulation of reddish-brown pigment granules at either pole of the nuclei of the atrophic muscle fibres.

FIG. 2
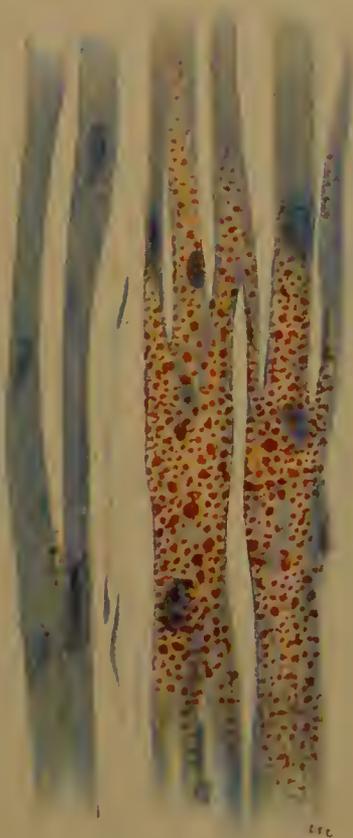
Fatty Degeneration.

Muscle fibres of heart from case of pernicious anemia, stained by Sudan III and hematoxylin to show fatty degeneration involving groups of muscle fibres.

What at first sight appears to be a like accumulation of fat in the form of minute globules, but without any nuclear degeneration, occurs *normally* in the cortex of the adrenal, and in the muscle cells of the uterus undergoing involution after parturition. On the contrary, with nuclear degeneration there may be large globules of fat in the cell, as happens in phosphorus poisoning. Histologically, it is therefore not safe to say that the minute globules indicate a degeneration and the larger ones an infiltration; there are evidently intermediate states.

Typical cases of fatty degeneration can be divided into: (1) those following cloudy swelling, therefore the second stage in parenchymatous

Fig. 98
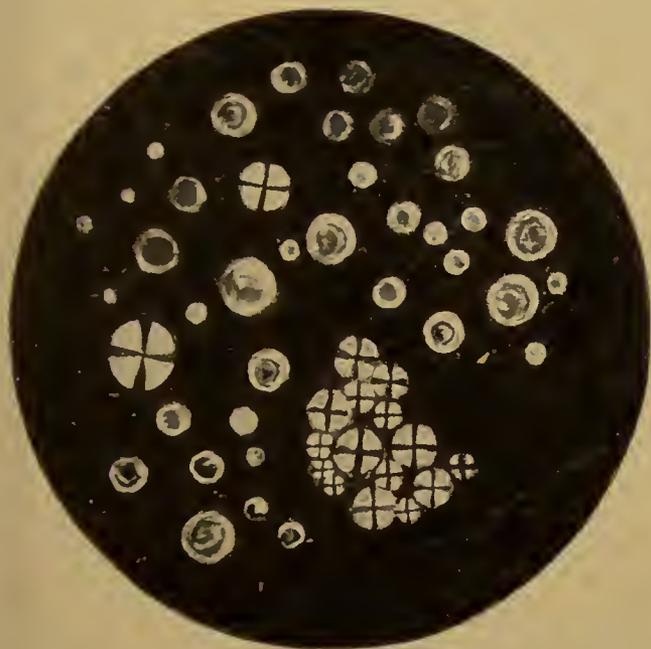
Fig. 99

Juice expressed from adrenal cortex, seen under crossed Nicol's prisms, showing isotropous fatty globules and anistropous myelin globules (with black cross).
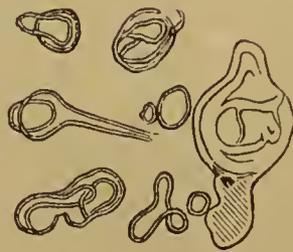
Double contoured myelin bodies of irregular rounded shape with processes. (Perls.) These myelin bodies are to be found in the morning sputum, and are lipoid in nature and doubly refractive.

inflammation of organs, and (2) simple uncomplicated fatty degeneration, (*a*) physiological, and (*b*) pathological. The first is exemplified in bacterial intoxications. Physiological fatty degeneration is seen in the cells of the sebaceous glands, and in the formation of the fat droplets of milk from the cells of the mammary gland, in which there is a multiplication of cells, those nearest the lumen becoming fatty and being disintegrated off as a mass of fat globules. Pathological fatty degeneration is seen in certain cases of acute intoxication that is not bacterial, such as poisoning by certain chemicals, and in the malnutrition of starvation or of the extreme anemias. There is no certainty, of course, that any or all of these fatty degenerations are not preceded by cloudy swelling.

Lipoid "Infiltration" and "Degeneration."—We have said that the appearance of the cells of the cortex of the adrenal appears at first sight to resemble fatty degeneration (see Plate VIII, Fig. 2). The work

of the last few years upon the lipoids has demonstrated that here we deal not with the accumulation of neutral fat but with globules which, unlike those of the neutral fats, are found doubly refractive under the polarizing microscope. Some neutral fat, it is true, may be present, but these characteristic globules are, according to recent investigations, formed in the main of cholesterin esters, more particularly of cholesterin oleate. Similar doubly refractive granules are found in very many parts of the body in degenerative processes, notably in the atheromatous patches of the aorta, in degenerating cancer cells, and in areas of degeneration in the nerve tissue. Chalatow has recently shown that by feeding rabbits with cholesterin abundant doubly refractile globules or fluid crystals of cholesterin esters appear in the liver, spleen, and bone marrow. But more than one of the lipoids can afford the appearance of double refraction.[1] One of the simplest and easiest examples of the existence of these doubly refractive so-called myelin droplets to study is in the sputum of adults coughed up first in the morning. It seems, therefore, that just as we may have a neutral fatty "infiltration" and "degeneration," so also we may have lipoid "infiltrations" and "degenerations." This subject is being actively studied at the present time, its chief interest lying in the relation between the lipoids and the proteins, many of the former resembling the nucleins in possessing both nitrogenous and phosphoric radicles, and suggesting strongly stages either in the building up or dissociation of bodies of the latter order within the cell.

Fig. 100
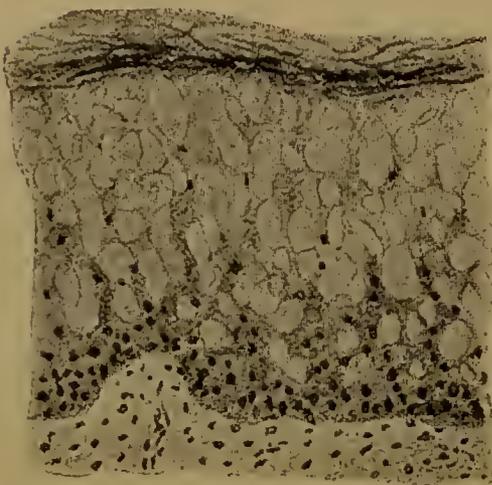
Hydropic degeneration; epithelium from a smallpox papule. The epidermal cells greatly swollen, distended by large vacuoles. × 300. (Ribbert.)

Glycogenous Infiltration.—We have little knowledge of the significance of glycogen in the tissues in abnormal situations or amounts. It is found in a considerable number of rapidly growing cellular neoplasms, as again in Henle's tubules of the kidney in cases of diabetes. It has been found also in pus cells.

Hydropic Degeneration.—Cloudy swelling being associated with an increase in the watery contents of the cell, there are extreme grades of this in which actual vacuoles appear in the cytoplasm; these watery vacuoles may increase in size till the cell bursts; the accumulated fluid from the bursting of several contiguous cells may then form vesicles. The most extreme examples of this are the "pocks" in smallpox, where the deeper layers of the epidermis become hydropic, swollen, and disintegrated.

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[1] See also page 26 for classification of lipoids.

PLATE VIII

FIG. 1
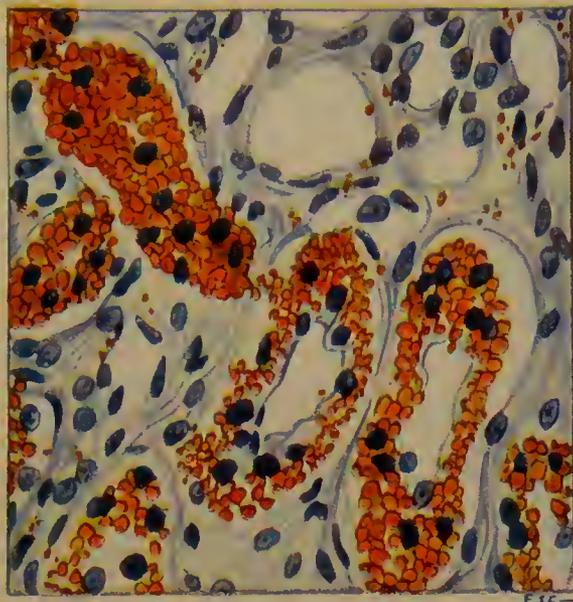
Fatty Degeneration.

Fatty degeneration of cells of the convoluted tubules of the kidney, from a case of acute, supervening upon chronic nephritis, stained by Sudan III and hematoxylin.

FIG. 2
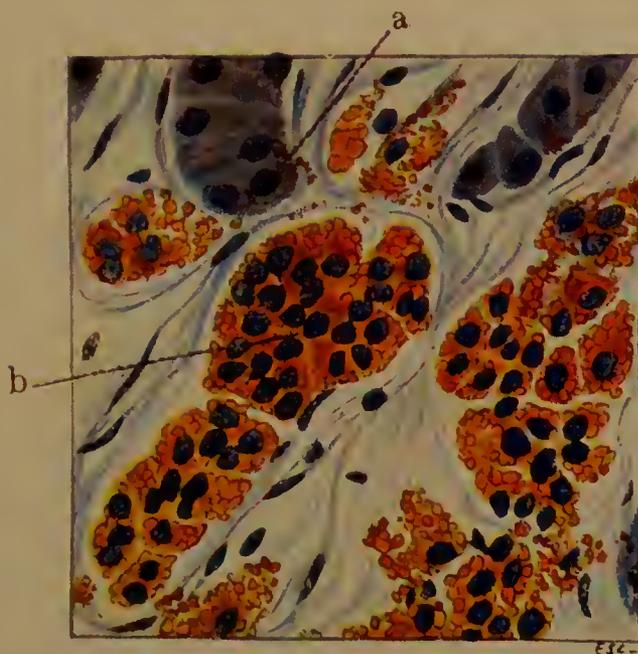
Lipoid Infiltration.

Cortex of human adrenal treated with Sudan III, to show accumulation of lipoid globules in the cells of the zona fasciculata. These globules are doubly refractive. a, cells free from lipoid globules; b, cell columns in which the globules are abundant.

The explanation of such absorption is that the colloidal outer layer of the cell, which represents the cell membrane of plants, ordinarily prevents the diffusion of crystalloid molecules; that crystalloid molecules do appear by some disorganization of the cytoplasm, and as long as these exist in the cell body in greater concentration than in the surrounding medium, water will diffuse inward until equalization occurs. Thus the cell swells up and becomes hydropic. In addition, Martin Fischer calls attention to the fact that increased acidity of a colloidal menstruum leads to an increased imbibition of water.

Vacuolar Degeneration is seen in muscle and nerve cells, and is characterized by the appearance in the cytoplasm of vacuoles, which are presumably caused by an osmotic absorption.

Serous Atrophy.—This has already been dealt with under atrophy; cells and intracellular tissue alike absorb a serous fluid which replaces preexisting fat.

DEGENERATIONS ASSOCIATED WITH THE DEPOSIT OF COMPOUND PROTEINS.—There is a series of ill-understood degenerations in which appears in the tissues material that in the unstained condition is translucent

FIG. 101
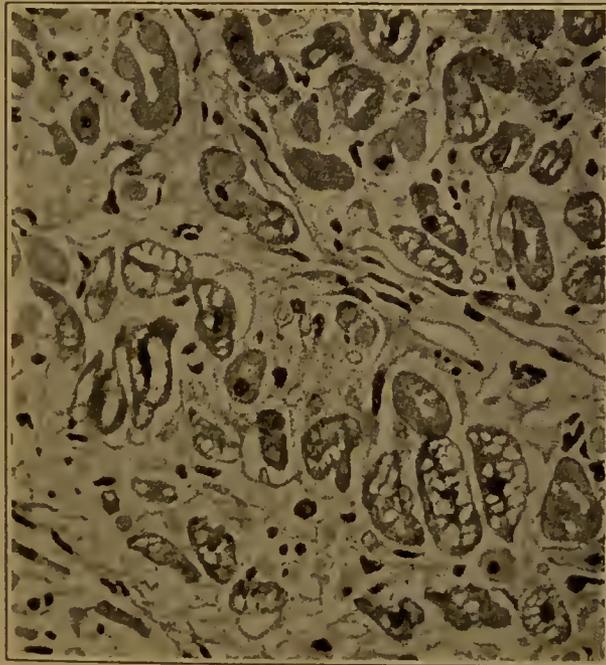
Hydropic degeneration of papillary muscles of heart which are cut transversely. The clear spaces indicate the vacuoles in the degenerated muscles. (Stewart.)

or glassy; when colorless and firm, we call this **hyaline**; when colorless and fluid or semifluid, **mucoid**; when semisolid or solid and of the appearance of glue, **colloid**. Hyaline and mucoid were once regarded as specific substances; but we know now that what is called hyaline, for example, may be produced in different ways. **Amyloid** is an exception, and from its staining reactions seems to be a separate entity. These substances are proteins; and in a molecule as large as even the simplest protein molecules are, it will be readily understood that a

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comparatively small change such as a few more or less carbon atoms or a few more or less oxygen atoms may be the cause of a considerable change in properties.

Mucoid Deposits.—Mucoid Degeneration and Mucinous Deposits.— The mucins are glycoproteins, compounds between protein and carbohydrate; they are laid down in the body **intracellularly** and **intercellularly**. Examples of the first are seen in the salivary glands and the goblet cells of the intestines, and of the second in Wharton's jelly in the umbilical cord and in the mucinous intercellular matrix of embryonic tissues in general. In either case, mucin is viscid, swells up with water, is soluble in weak alkalies, and is precipitated by acetic acid or by alcohol. Basic dyes stain it.

Intracellular Mucin Formation.—Mucin is thus produced in catarrhal states of mucous membranes, in which not only is there active production of mucin by goblet cells, but also a degeneration of individual cells, including the nucleus, by which the entire cell substance changes to mucin. Mucin as such does not appear in the healthy cell, but mucinogen, its precursor, may, and mucin production occurs with a previous process of cell division which is like that seen in secretion in the mammary gland. A more active production is that seen in the so-called **colloid** cancers, an unfortunate term, as the material is inspissated mucin; these growths originate from the intestinal mucosa, the tumor cells undergoing a complete transformation into mucinous matter.

Intercellular or Interstitial Mucin Formation.—This may be found pathologically in:

1. Senile atrophic tissues, as in the cartilages and bones of the old.

2. The connective tissues in the early stages of myxœdema. It was at first thought that increased interstitial mucin was a constant change in the subcutaneous tissues in atrophic diseases of the thyroid, but in long persisting cases the mucin is found to diminish with coincident development of fully formed connective tissue.

3. Actively developing tumors of the connective-tissue type, sarcomas, fibromas, and in the interstitial tissue of carcinomas. Mere œdema of tumors is often mistaken for a mucoid degeneration.

4. Developing granulation tissue.

In all these circumstances it will be seen that we deal with either active tissue, or with immature tissue, or with tissue reversion.

Colloid.—Dense colloid deposits are relatively rare. The typical example is the gluey or almost solid accumulation within the distended vesicles of the enlarged colloid goitre; similar material may show itself in vesicles of the pituitary. The next most common site is in the urinary tubules in certain cases of chronic nephritis, the tubules becoming plugged with dense hyaline, or more accurately, colloid casts which take on a deep stain with the ordinary staining reagents.

Amyloid.—This is a material allied to the matricial matter of cartilage, but not found in normal tissues. When it is present, it has a characteristic appearance and well-marked individual reactions. It may be

generalized, affecting several organs, or localized, affecting a relatively small area of inflammatory or neoplastic growth.

Generalized Amyloid; Amyloidosis.—When advanced, this affects a large number of organs, especially the spleen, liver, and kidneys. The only tissues that have not been found affected are the epidermis, the cutis, bone, lung tissue, and nervous tissue proper. If the spleen and liver be free, it is useless to search other organs for it. The affected spleen is enlarged and more dense and firm than usual. On section it has a semitranslucent, waxy appearance (hence the terms **waxy** or **"bacon" spleen**), this being diffuse; or rounded areas are seen on the cut surface of the size and appearance of sago grains (**"sago spleen"**) the affected parts being the Malpighian bodies. The appearance of the liver and of the kidney is by no means so characteristic, but the reactions can be readily demonstrated.

Fig 102
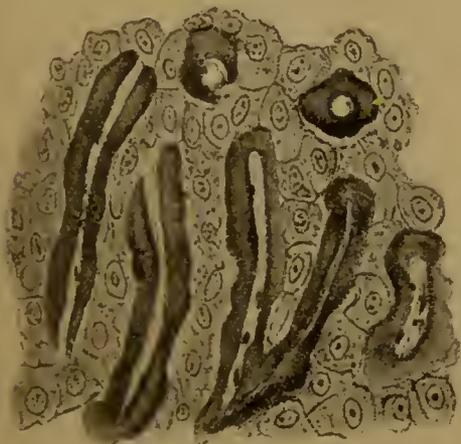
Fig. 103

Amyloid degeneration affecting the liver; slighter grade; the cells are still present with but moderate atrophy; the irregular deposit of amyloid around the capillaries is well marked. (After Ribbert.)

Amyloid degeneration of liver, advanced: *a*, atrophied liver cells; *b*, transverse section of a capillary surrounded by a broad ring of amyloid material; *c*, a capillary cut longitudinally. (Ribbert.)

Reaction.—On the cut surface of the organ washed free from blood is poured diluted tincture of iodine. When the surface has assumed a pale yellow tint the amyloid will have a brownish-red color; if now a 5 or 10 per cent. solution of sulphuric acid be poured on, the amyloid becomes violet or black, the rest of the tissue remaining relatively unaffected. The same method may be applied to the microscopic examination of sections cut from the frozen tissue, the affected parts showing clear and yellowish by transmitted light. Even more distinctive in sections is the use of watery methyl violet, followed by washing in very dilute hydrochloric acid; this applies to fresh or alcohol-preserved material, and shows the amyloid as a rose-pink mass against a slaty background.

The deposit of amyloid occurs in the walls of the capillaries, just external to the endothelium, and in the larger vessels the connective tissue of the media is the part affected. The amyloid is laid down

quite irregularly, so that a vessel may look lop-sided by reason of this inequality. The results to the tissues of the laying down of amyloid are twofold: the lumen of the vessel is encroached upon, and the tissues are thus ill-nourished, as well as subjected to pressure by the physical presence of the amyloid; ultimately the original tissue may be almost destroyed. Amyloid deposits are made in the body during the course of long-continued drains upon the system, especially when this is associated with an excessive production and an excessive waste of leucocytes, although a protein discharge of any sort will produce the effect. Chronic bone tuberculosis with cold abscess, osteomyelitis, syphilis, leukemia, Bright's disease, or even prolonged lactation are some of the states that produce it.

Localized Amyloid.—This is seen in localized granulomatous masses of tuberculous or syphilitic origin and in connective tissue tumors, especially of the head and neck region. In such sites the small blood-vessels are relatively unaffected, the amyloid being laid down in the interstitial tissue, perhaps along the lymph channels.

The Nature of Amyloid. The blue color with iodine and sulphuric acid led to the supposition that amyloid was related to starch, whence its name; but its protein nature was soon shown, although the name persisted. It is a glycoprotein, containing chondroitin-sulphuric acid. This material, brought by the blood or lymph, probably diffuses out through the walls of the vessel and meets a local protein with which it combines. In composition it is somewhat allied to the chondrin of cartilage and yellow elastic tissue, which also contain chondroitin-sulphuric acid. Thus **chondroid**, rather than **amyloid**, would be the accurate term.

Elastoid.—We have separated from the group of hyaline degenerations another form seen often in the uterus after delivery and involution, in which, especially at the region of the placental site, arteries more or less obliterated are to be recognized as glistening, hyaline masses. The recent studies of our colleague, Dr. Goodall, have shown that, associated with the narrowing of the lumen of the much-dilated vessels, the internal elastic lamina undergoes a most remarkable process of swelling and folding upon itself. At first the swollen elastic tissue reacts with Weigert's elastic-tissue stain; in a later stage it no longer gives this reaction. The remarkable fact is that within these swollen masses a newer, smaller arterial lumen is developed, which may become surrounded by all the arterial coats, intima, media, and adventitia, whereas to the outer side, the previously hypertrophied media undergoes complete degeneration and absorption. In this way the arteries adapt themselves to the lessened demand for blood by building what may be an entirely or partially new artery within the lumen of the old.

Hyaline.—Of the other orders of hyaline, which still retain this name, the commonest is that found, apparently as a persistent necrobiotic stage, in association with connective tissue, though other tissues also may be involved. Examples of this are to be seen in the connective-tissue framework of the thyroid and kidney in cases of so-called chronic

PLATE IX
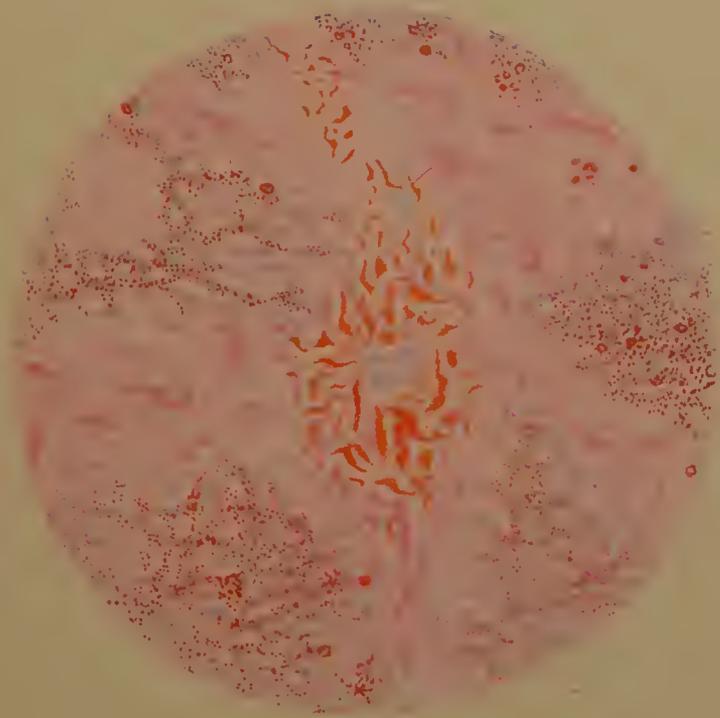
Fatty and Amyloid Degeneration of Liver.

The liver cells show fat stained by Sudan; the pink areas are amyloid, while in the central part of the field there is a heavy deposit of fat which represents an extremely fatty liver substance which has not been replaced by amyloid. (Professor Oskar Klotz.)

interstitial inflammation. Here relatively large tracts of thickened fibrous tissue may assume a glassy appearance with great paucity of nuclei. Some of the largest areas are seen in the myocardium in cases

FIG. 104
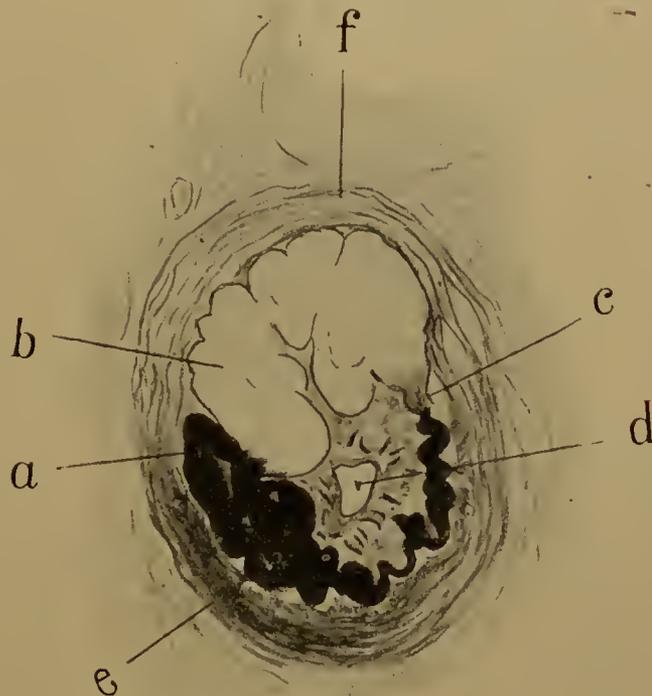
Elastoid degeneration: Section of small artery from beneath placental site of uterus exhibiting subinvolution. The patient suffered from renal and hepatic disturbances, and died seven months after delivery. Section stained by Weigert's elastic and Van.Gieson's stains. (Dr. Goodall.)

Hypertrophy of elastica interna at *a;* vitreous degeneration of the same at *b;* at *c,* transition from stained hypertrophic to unstained degenerated elastica; *d,* lumen of the new vessel surrounded by irregular new muscular and intimal tissue; at *e,* remains of old media with hypertrophy of its elastic fibres; outside the degenerated elastica interna at *f* the atrophy of the media is more extreme.

FIG. 105
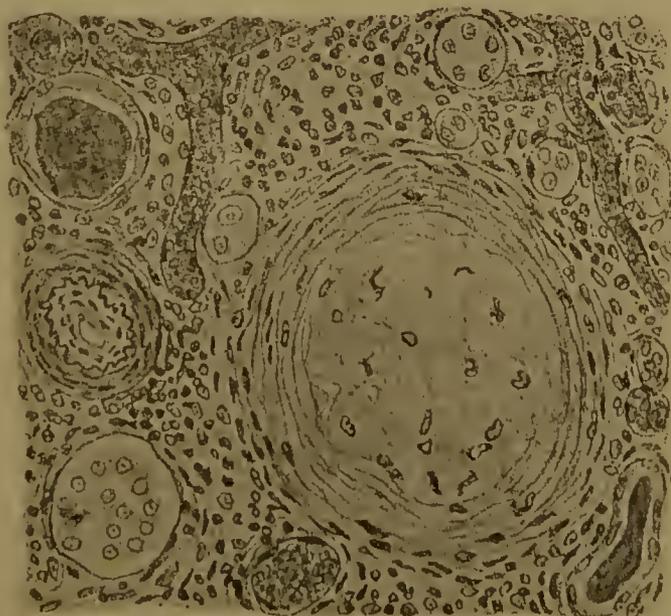
Hyaline degeneration of a glomerulus, from a kidney showing chronic interstitial nephritis.

of so-called chronic myocarditis in the form of irregular areas of hyaline matter interposed in the mass of still unchanged muscle tissue; possibly here we deal not merely with a change in the fibrous tissue which has replaced dead muscle fibres, but with a hyaline transformation also of muscle cells whose nutrition has been cut off through obliteration of the arterioles. In several orders of tumors there is a similar hyaline necrobiosis of cells farthest removed from the nutrient vessels; these tumors then assume the appearance known as **cylindromatous.** A like hyaline change may also affect the organized fibroid deposits on serous surfaces, the new connective-tissue growths of granulomas and even capillary walls. Of this last, the most noticeable example is seen in the hyaline clumps which represent the glomeruli in cases of chronic interstitial nephritis (Fig. 106).

FIG. 106
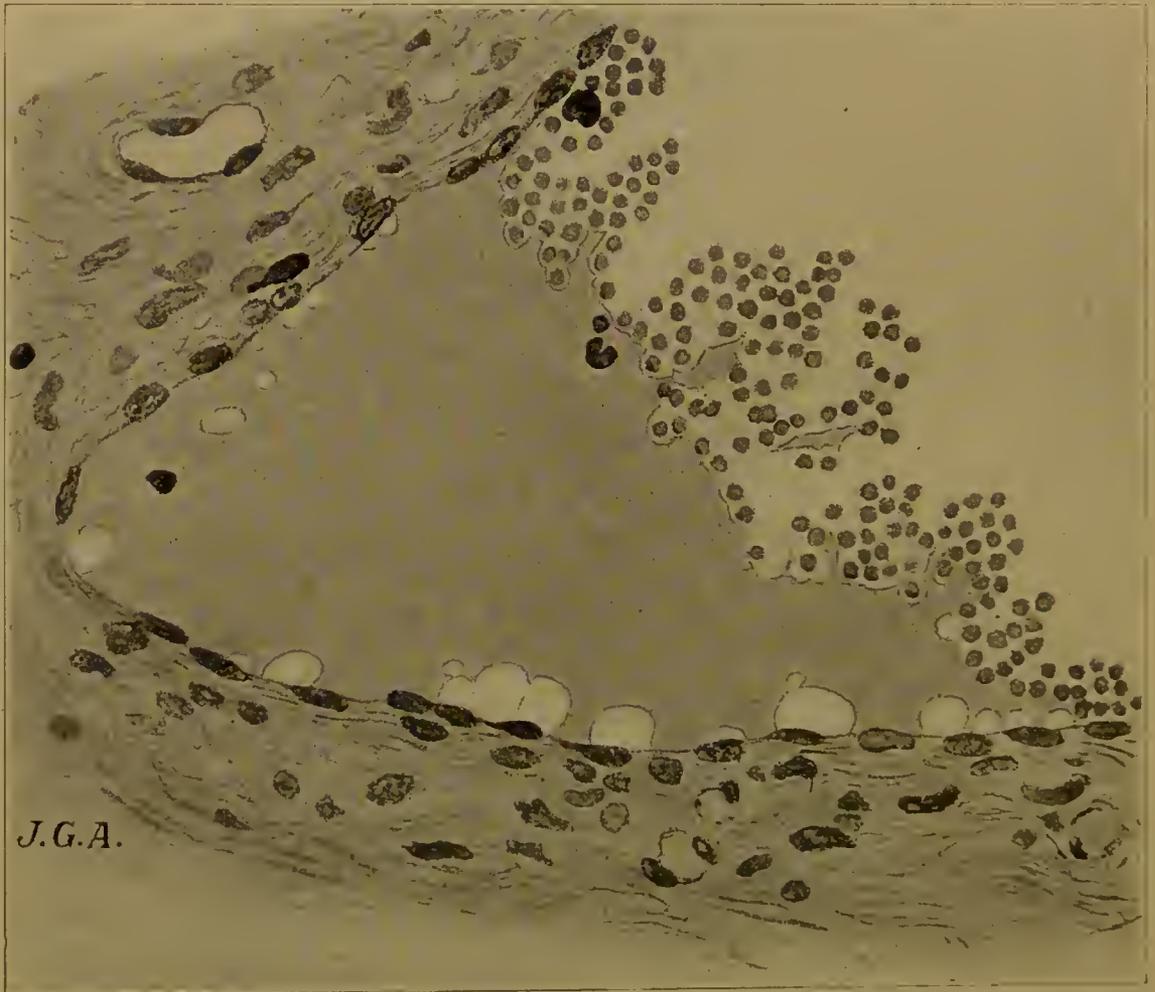
Hyaline thrombus in dilated venule of hemorrhoid. This was perfectly homogeneous. Reichert, obj. 7a, ocular 4. Camera lucida, reduced one-third.

Hematogenous Hyaline (Hematohyaloid).—Of this form the type example is seen in hyaline thrombi due to the intravascular and intravital conglutination, either (*a*) of the entire red corpuscles, as under the action of agglutinin, or (*b*) of the same after a preliminary disintegration into smaller globular masses, or (*c*) of blood-platelets. Occasionally, a fibrinogen-containing serous exudate, instead of forming the char-

acteristic fine fibres of fibrin, undergoes coagulation in the form of homogeneous hyaline masses. This seems to be an allied condition.

Hyaline Casts.—There is still debate regarding the mode of origin of the transparent, scarce visible casts seen in the urine. Some authorities regard them as the result of coagulation of constituents of the blood escaping into the tubules, and in favor of this view there is that at times these have been seen in parts to take Weigert's fibrin stain. Others regard them as more commonly the result of fusion and inspissation of discharges or broken-down matter from the epithelium of the tubules. Where there is more extensive disintegration with liberation of coarser portions of the cell, a **granular** cast is produced; where the entire cells in the course of acute inflammation become cast off, there is formed the **cellular** or **epithelial** cast. It is possible that a mass of cells lying as a cast in the tubule may undergo further change, a cellular thus becoming a granular or perhaps even a hyaline cast. Where the disintegrated material detained within the tubule undergoes progressive inspissation, there is developed the **colloid** or **waxy** cast.

Intracellular Hyaline.—Especially in the study of cancers there have been noted small globular or irregular masses within the cells, having the appearance and reaction of hyaline. A series of cases has been described showing various gradations of staining power (and therefore of chemical composition). Of these the most familiar examples are the **Russel's fuchsin bodies,** so-called because they fix fuchsin with considerable intensity. These originate, apparently, within the cell in cases not merely of cancer but also of chronic inflammation. Often through degeneration of the cells they come to be extracellular.

Pathological Keratinization.—This is an allied condition. The normal epithelial cells of the skin, as they come to lie farther and farther removed from the Malpighian layer, exhibit when they reach the level of the stratum granulosum fine granules of **keratohyaline.** These stain blue with hematoxylin. In the stratum lucidum these become translucent and are seen to be evenly diffused throughout the cells (**eleidin**). Further outward is to be seen a second development of granules of **keratin** which take on a purplish-blue color with Gram's stain. Passing still farther outward, as the cells become completely necrotic, with non-staining nuclei, they become represented by flattened scales of compact keratin; this stains yellow with van Gieson's stain. Occasionally we encounter massive accumulations of these keratinized cells, as for instance in the middle ear, forming pearly masses known as **cholesteatoma,** and in the cutaneous **horns** which may show themselves on one or other area of the body surface. These are not true hypertrophies, but abnormal collections of matter not properly cast off. At most, the underlying rete Malpighii may show hypertrophy and indications of increased cell proliferation.

Rare allied conditions are those of **hyperkeratosis** and **ichthyosis,** acquired and congenital imperfect growth of the skin accompanied by thickening of the keratin layer. Chronic irritation sometimes leads the

tongue to present keratinized processes of the epithelium (**hairy tongue**), the œsophagus to exhibit longitudinal bands of epithelial thickening (**leukoplakia**), this notably in alcoholics, and the vagina to show horny ridges (**pachydermia**).

CALCIFICATION AND CALCAREOUS DEPOSITS

Almost every order of tissue may be the seat of interstitial deposits of calcium salts, although the supportive tissues, such as cartilage and the connective-tissues of vessels and of organs, are most frequently affected; the parenchyma of glands is at times liable to it and deposit may occur intracellularly in the nervous system. The extent of the deposit may vary between a few gritty particles in a mass of caseation to large masses as dense as stone. The deposit of calcium salts has little in common with the process of ossification, although in this, too, calcium salts are the material that is laid down; there are none of the orderly processes by which in bone the calcium salts are related to the blood-vessels and the matrix; although, according to Wells, there is a striking similarity in ratio between the calcium and magnesium salts and the phosphoric and carbonic acids that exist in bone and in pathological calcification.

Microchemical Appearances and Reaction.—In the smallest masses the calcareous deposits are like fine dust, which may give place to angular, crystalline masses or even globular concrements. Insoluble in ether or caustic potash, they dissolve rapidly in acids and slowly in formalin, and when dissolved out, a matrix of dead tissue is left in which histological characters are not to be distinguished. Stained with hematoxylin, calcareous material takes a pronounced dark blue color. Treated with a 5 per cent. solution of silver nitrate for five minutes, with subsequent exposure to the air, metallic silver is precipitated, causing the granules of calcareous material to stand out as coal-black dots, in consequence of the action of the phosphates present. Treated with acid, there is an evolution of bubbles of gas—carbon dioxide—indicating the presence of calcium (and magnesium) carbonates. Sulphuric acid causes the appearance of fine crystals of calcium sulphate (gypsum).

Calcification may occur in tissues that contain living cells, *not in the living cells themselves, but in the inert interstitial matter between the cells;* it occurs, that is, in dead or necrescent material, and the statement may be made that it does not occur in living functioning cells. The statement that calcareous deposit does not occur in living cells is made with a knowledge of the apparent exceptions.

It may be said, then, that calcification occurs in dead or dying cells, and in certain interstitial substances such as the matrix of cartilage, yellow elastic tissue and hyaline, this latter change being especially allied with other senile alterations. Belonging largely to the former group are those instances that happen in the interstitial tissue of

glandular organs like the thyroid, the testes, or the ovaries, in the lungs, the membranes of the brain, and in scars, and most of all in the arterial walls. In the arteries, calcareous deposit follows hyaline and fatty degeneration (**necrobiosis**) of the media and the hypertrophied intima, and also in the elastic tissue; these changes may be shown by the specific tests when no change is apparent to the naked eye. Equally liable to give examples of such calcification are old infarcts, chronic inflammations of the serosæ, of the walls of cysts, and of capsules around foreign bodies, while the existence of calcification in old inspissated suppurations is often seen. A perfect example is seen, too, in the impregnation with lime salts of the dead fœtus, the result of an extra-uterine gestation retained in the abdominal cavity (**lithopædion**). Experimentally, there are many chemicals which cause calcareous deposit; this action has been studied chiefly in the kidneys, where the deposit is preceded by a bionecrosis of the tubular epithelium.

Different hypotheses have been brought forward to explain the phenomenon of calcification, of which the most satisfactory appears to be that specially elaborated by the work of our former colleague, Klotz. Obviously, it is not a precipitation of the salts normally present in the affected areas; the lime salts are brought to the part by the lymph, and in dead or dying cells or in the interstitial material of low vitality are rendered insoluble and deposited. The chemical process underlying this appears, in some cases at least, to be that a fatty degeneration of cells is accompanied by the liberation of fatty acids, which combine with the calcium in the lymph to form compound calcium soaps. In this combination the weaker fatty acids are replaced by phosphoric and carbonic acids, with the subsequent deposit of insoluble calcium phosphate and carbonate in the dead tissues. The compound calcium soaps are probably compounds of fatty acid, calcium, and a protein or a product of protein disorganization.

FIG. 107

Section of aorta of elderly individual, treated by von Kossa's method, to demonstrate calcification of media, and more particularly of the muscular bands. (Klotz.)

In a later work on this subject Professor Wells, of Chicago, while admitting the foregoing, regards it as the more uncommon mode, and brings forward not a little evidence to show that hyaline cartilage and homogeneous hyaline degenerative material possess an affinity for calcium not exhibited to an equal degree by other tissues, so that in favoring circumstances the calcium salts are "absorbed" by the

colloidal scleroproteins from the lymph until they come to be in such concentration that they are precipitated in the same proportions as those in which they exist in the circulating medium. He admits, however, that the factors concerned in this process of precipitation are not wholly known, suggesting that possibly a reduction in the amount of carbon dioxide or some other agency induces the precipitation of calcium salts in a colloid matrix.

Concrements.—In addition to this deposit of calcareous material in the tissues, there may be a deposit of the same in ducts or passages, leading to the formation of solid masses, round or oval or taking the shape of the duct in which they are found. These are termed **concrements** or **calculi**, the same term, unfortunately, being employed both for the above calcareous deposits and for deposits due to the abnormal precipitation of specific excretions. Concrements of the first order will be found to contain an amount of calcareous salts in excess of that usually present in the fluids discharged along the passage concerned. On dissolving out the salts, there is left a matrix of mucinous material, usually mixed with fatty acids, soaps, and cholesterin. Such concrements arise generally as a result of a catarrhal inflammation of the passage in question, whereby mucin is exuded and some of the cells exfoliated. The disintegration of the latter affords the products of proteolysis and the fatty material, and in this as a matrix, just as in necrotic tissue, there is a deposit of calcium salts, by diffusion into the mass, of serum from the inflammatory exudate and of the secretion normal to the passage. Of these concrements, the following are worthy of note: **rhinoliths** in the nasal passages after ozena; **tonsillar** concrements formed in the crypts; **salivary** concrements formed in the salivary ducts; **lacrimal**; **cutaneous** (formed in sebaceous ducts); **preputial**, following phimosis, with accumulated smegma as a foundation; and **appendical** concrements which have as a base rolled up and compressed fecal matter. **Pancreatic** concrements are of widely varying constitution, this depending probably upon the length of time during which the concrement has been retained; a recent one will show abundant products of cell-disintegration, while an old one will be largely composed of insoluble salts, a distinction which may be considered to hold not only for pancreatic but for all concrements.

Phleboliths.—These are small oval stones formed in veins, chiefly in the uterine plexus in the female, and the prostatic plexus in the male. All transitions may be found from a comparatively soft to a hard pearl-like body; the phlebolith arises from the deposit of lime salts in isolated thrombi that have not undergone organization, and thus lies free in the lumen of the vein.

Calcareous Incrustations.—Deposits of various kinds upon surfaces may undergo a similar impregnation with salts derived from the body fluids. The commonest example is the **tartar** of the teeth, of which epithelial debris and particles of food form the foundation; in chronic cystitis a deposit of phosphates may occur upon the mucosa, while

foreign bodies in the tissues or cavities of the body are apt to become similarly encrusted.

Calculi or concrements of the second order include four groups— *urinary, biliary,* and *prostatic calculi,* and *corpora amylacea.*

Urinary Calculi.—**Urinary Lithiasis.**—Any of the usual or unusual salts of the urine may be precipitated to form calculi, and for this formation certain features must be present, which are common to all different forms of calculi. The calculus must have a **nucleus** of mucus, of cell-debris, or of foreign matter, such as blood clot or an introduced foreign body, in and upon which the salts are deposited. The rate of this deposition will depend upon the relative amount of salts present in the solution, that is, the concentration of the salts; as in the urine this is very variable, the rate of deposit also varies, so that periods of progression of deposit may alternate with periods of arrest. As a consequence, most calculi are seen to be formed of **concentric laminæ.** Since, too, in the urine, at one time one salt may be present in excess, at another another, it generally happens that layers of more than one sort enter into the formation of a calculus; mixed calculi are the rule rather than the exception; and in urinary calculi, the growing stone acting as an irritant, infection occurs with production of alkaline urine, so that the most superficial layers may be phosphatic in nature.

The mere presence of salts in excess in the urine is not adequate to explain calculus formation. If the salts be dissolved out of the calculus, there is left behind a matrix of organic matter of gelatinous or colloid type, yellowish or otherwise pigmented; and if calculi be ground down to make sections, after the manner of the geologist, it will be found that the salts are not laid down in their usual crystalline form, a fact which had been previously noted in egg-shells, bone, etc.; this appears to mean that there is first of all a mucinous or colloid matrix laid down, and that crystallization in colloidal solution greatly modifies the shape of the crystals, the crystals tending to be rounded instead of angular. Such a mucinous or colloid material is thrown off in inflammatory states, and the greater its amount, the greater is the liability to precipitation of the salts. Thus for the formation of urinary calculi it seems necessary to have three factors: (1) the presence of a crystallizable body in excess in the urine, and (2) irritation of some part of the tract leading to increased discharge of mucinous material, and (3) some solid body which will act as a nucleus on which precipitation occurs. The irritation need not be bacterial, but no doubt it is so in a considerable number of cases, and if not so at the outset, the irritation caused by the stone will readily lead to a passing infection being picked up.

The most important groups of urinary calculi are the uratic (including uric acid), those formed of calcium oxalate, and the phosphatic.

Uric Acid and Uratic Calculi.—Uric acid is the commonest constituent of calculi, whether as the main or as a subsidiary salt, and is more common as uric acid than as amorphous urates. The typical uric acid calculus is rounded or oval; its surface is smooth or finely mammillated;

the color varies from fawn to red, according to the amount of uroerythrin which is brought down in the urine when uric acid separates out, and on section the stone is laminated (Figs. 108, 110). These occur relatively frequently in early life, and appear to originate in the pelvis of the kidney, whence they may be passed while still small, as **gravel**, small calculi of a reddish tinge. Remaining in the pelvis of the kidney they may there undergo increase in size, until they form a "staghorn" mass, accommodated to the shape of the pelvis of the kidney and its branches.

FIG. 108.
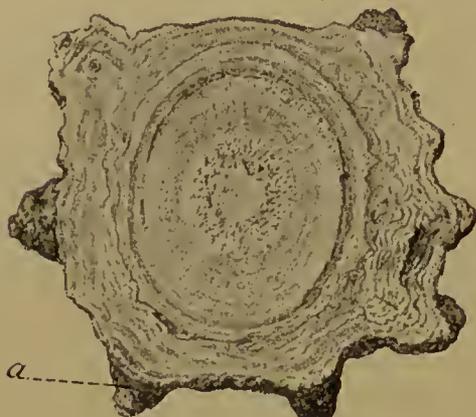
FIG. 110.
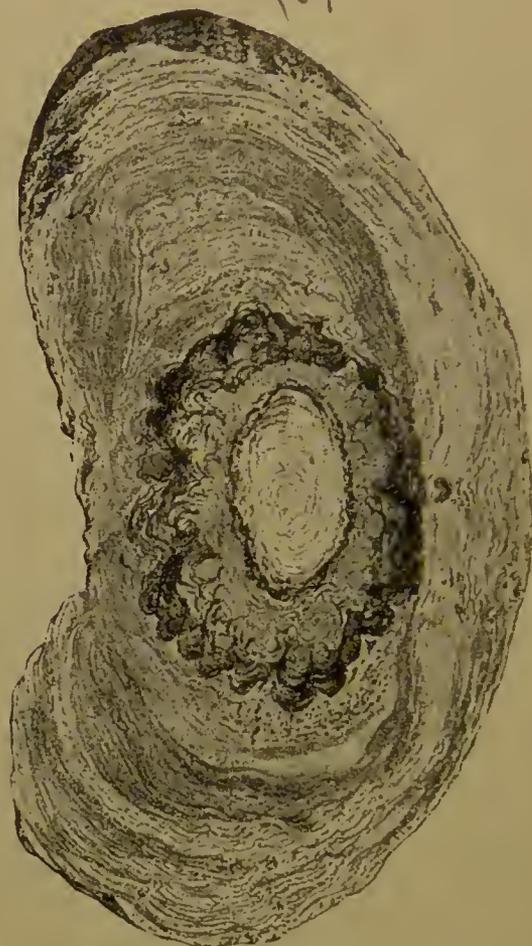
FIG. 109.

FIG. 107.—Calculus formed of uric acid followed by oxalate; appearance on section.
FIG. 108.—Oxalate of lime calculus ("mulberry" calculus), exterior view.
FIG. 109.—Ammonium urate followed by oxalate and eventually by mixed phosphates   (These three figures are from the catalogue of the Royal College of Surgeons.)

Uratic Inspissation in Infancy.—Autopsies upon infants a few weeks old frequently show the calices of the kidneys opaque and whitish or even definitely streaked with yellow, while in the pelvis a few reddish-brown grains can sometimes be collected. The collecting tubules contain a large number of minute doubly refracting spherical masses of urates in a mucinous matrix, and the condition has been usually called **uric acid infarct**, a less suitable term than **uratic inspissation**; the masses, chemically, are composed of quadriurates. Why there should be a relatively great discharge of uric acid and urates in the very young is

not understood, but there seems good reason for supposing that masses of this sort are in part responsible for the uric acid calculi frequently found in the young.

Calcium Oxalate Calculi.—The most commonly seen of calcium oxalate calculi are those that are called "**mulberry calculi.**" There is a "bossed" or mulberry-like appearance with brown or black color, and on section the laminæ appear laid down like the plan of a fortress with bastions (as shown in the outer part of Fig. 108). In composition it is found that most of the oxalate calculi contain uric acid, with substances deposited from acid urine.

Fig. 111

A stag-horn calculus (*a*) in pelvis of the kidney.

Phosphatic Calculi.—These may be formed only of calcium phosphate, or of ammonium magnesium phosphate, or of pure ammonium phosphate; of these the mixed form is the most common. All are thrown down from alkaline urine, and if the alkalinity depends on sodium salts, the calcium phosphate stone is found, whereas if the urine has become alkaline from infection and fermentation the triple phosphate is likely to be found, giving rise to a stone that is of loose cohesion and friable, but which may be of large size.

Other Urinary Calculi.—Cystin calculi, of a pale yellow color, becoming green on exposure to light, and of soft consistence, and **xanthin** calculi, although very rare, are known. **Guanin** calculi have been described in cattle, as well as **steatoliths** of fatty or soapy masses in man.

Biliary Calculi; Cholelithiasis.—The composition of biliary calculi brings it about that they are less dense and lighter in weight than the urinary calculi; they are composed of modified bile pigments, cholesterin, and at times, calcium carbonate.

Classification.—1. **The Common Gallstone.**—This may be single, large, and barrel-shaped, the ends being facetted, or there may be a small number of relatively large stones facetted to one another, forming together a cast of the gall-bladder; or there may be multiple small stones, even hundreds in number, all of relatively the same size, generally facetted, the facetted surfaces smooth. The color varies from black or deep brown through reddish-brown (**bilirubin**) to green (**biliverdin**), or may be pale yellow from superficial layers of cholesterin or white from calcium carbonate. The cut surface shows concentric

layers of varying color depending on the extent of admixture with the calcium salt of biliverdin or bilirubin; the nucleus is often of cholesterin.

2. *Pure (or almost pure) Cholesterin Calculi.*—These are not very common, and are usually single, oval, pale yellow stones, with a waxy-looking, finely nodular surface. When broken, the surface is crystalline-looking, and there is little or no sign of stratification. It is quite rare to find them absolutely pure, but 95 per cent. or more of the contents may be cholesterin.

Fig. 112

Section of common mixed bilirubin calcium gallstone. (Naunyn.)

Fig. 113

Cholesterin calculus, cut and polished to show radiate crystalline structure. (Naunyn.)

Fig. 114

Section of "amorphous" cholesterin gallstone exhibiting central cavitation. (Naunyn.)

Fig. 115

Pure bilirubin calcium calculi; bile gravel. (Naunyn.)

3. *Pure Bilirubin Calcium Calculi.*—These are sometimes termed "bile gravel," and are multiple blackish granules, lying in mucoid bile; when fresh they are soft, and break under the finger; when dry they crumble apart.

4. *Calcium Carbonate Calculi.*—Comparatively rare, these stones are very hard; more often nodules of calcium carbonate occur in the mixed calculi, or common gallstones.

Etiology.—In the difficult problem of determining the causes of gallstones, there are certain well-recognized facts at the outset, such as these: that they occur most often in or after middle life, in females oftener than males, and in those of sedentary rather than of active

habits; and that the cholesterin of which they are formed is not excreted to any extent by the liver, but from the mucous membrane of the gall-bladder and the bile passages, especially the former. The increased production of cholesterin is due to a catarrhal state of the gall-bladder

Fig. 116
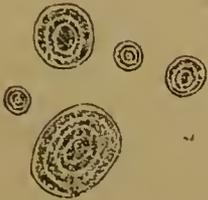
Corpora amylacea from brain, to show laminated character.   × 250.

Fig. 117

Section through an amyloid body from a sternal tumor, yet more highly magnified, to show the subcrystalline deposit of successive layers of closely packed needles of amyloid material.   At *a* the needles radiate from a small focus.   (Ophüls.)

Fig. 118
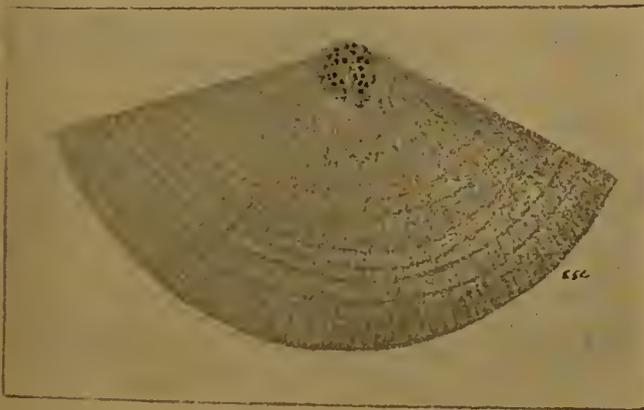
Amyloid body from lung (immersion lens) to show radiate crystalline formation similar to that seen in figure preceding.

Fig. 119
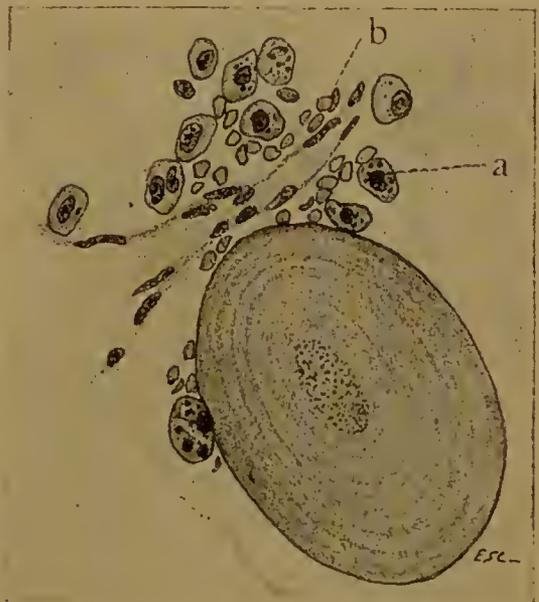
Amyloid body lying in a pulmonary alveolus from a case of chronic passive congestion of the lung (high power): *a*; large "cardiac" cells, containing pigment, *b*, red corpuscles.

wall, induced by some bacterial agent, often of a low grade of virulence; the readiness with which the gall-bladder is infected in general blood infections, such as typhoid fever, will be recalled in this connection; finally it is necessary for such a state of affairs that the bile be stagnant,

the contents of the gall-bladder not being quickly drained and as quickly renewed.

In gallstones, as in urinary calculi, is a mucinous matrix in which the salts are deposited, and such mucinous matrix, here also, indicates that for their production there must be a catarrhal condition of the gall-bladder, with increased outpouring of mucus into the bile. The studies of the last few years have shown us with increasing emphasis the frequency with which organisms of low virulence, notably the B. coli and B. typhosus, exist for long periods in the gall-bladder. It has been shown, indeed, that cultures of one or other of these organisms added to sterile bile leads to a deposit of all the constituents of gallstones. Thus, both by favoring a low form of catarrh and by acting on the bile, these, and other organisms, directly lead to the production of gallstones. As to the cause of the great variation in the relative amounts of the different constituents we are still in doubt, but pure cholesterin calculi are most frequently found in cases in which, through obstruction, the gall-bladder or its duct is cut off from the flow of liver bile. Their cholesterin appears thus to be derived mainly from the mucous membrane lining the gall-bladder (and ducts). Possibly these pure cholesterin calculi differ from the other forms in not being due to bacterial irritation, but merely to the accumulation of cholesterin in the blocked gall-bladder. The deposit of calcium salts appears to be associated with the breaking down of cellular debris, as in other concrements.

Prostatic Calculi.—Section through the prostates of most men past middle life shows the presence of minute, dark-colored granules in the substance of the organ; these are sometimes called **prostatic sand.** They are situated within the lumina, are hyaline-looking, generally polygonal, and of concentric structure; they are so soft as to be capable of cutting, and give imperfectly the reactions of amyloid; they are sometimes called **amyloid bodies** of the prostate, and one of them may be the nucleus for the incrustation of salts.

Corpora Amylacea.—Closely allied to the last are minute concretions found in the brain and spinal cord of the old, in lung alveoli in cases of chronic congestion with hemorrhagic discharge into the alveoli, and in certain tumors. They have the general appearance of hyaline material. The growth of some, at least, of these bodies in the lungs and in tumors is by successive deposit of layers of crystalline needles of protein nature (Figs. 117 and 119).

PIGMENTATION AND PIGMENTARY CHANGES

Their relative unimportance is the chief excuse that exists for grouping the pigment changes of different sorts together, because the possession of color is no adequate ground of relationship. The pigments can be divided according as they are: (1) endogenous, that is, are the direct products of cell metabolism or disintegration, or (2) exogenous, that is, are colored matters foreign to the organism and

absorbed from without. The endogenous we may further divide into (*a*) hemoglobin and its derivatives, and (*b*) other metabolic pigments.

Endogenous Pigments.—Abnormal Pigmentation Due to Hemoglobin and its Derivatives.—It will be remembered that hemoglobin occurs in a soluble form in the blood corpuscles, and especially in the portal system (including the spleen) is disintegrated, by the liver cells especially, with discharge into the bile of the iron-free portions of the pigment as bilirubin and other bile pigments. The urinary pigment, urochrome, is probably also derived from it.

Experimentally, by many chemicals, by foreign blood serums, and other agents, such as thermal changes, the red corpuscles can be broken up and the hemoglobin freed into the serum, whence it diffuses into the tissues and is absorbed by various cells. In diseased states, especially sepsis, **hemoglobin imbibition** occurs, the heart valves and the surface of the aorta showing a bright-red color from absorption of the pigment, a condition to be distinguished from postmortem change of the same tissues; in sepsis the staining is partly ante mortem. When the pigment is set free in the blood in large amount it may quickly appear in the urine, unaltered as in **hemoglobinuria** or modified as in **methemoglobinuria**, in the latter having a firm combination with the oxygen with an acid reaction. If the red cells are destroyed in the tissues or serous cavities, the pigment before its discharge may undergo a further change into hematoidin or urobilin and be excreted as such (**urobilinuria**).

Paroxysmal hemoglobinuria is marked by the sudden appearance of hemoglobinuria for a short time, after which again the urine becomes limpid. With some people exposure to cold is enough to excite the state, and the attacks are most frequent in winter, the red corpuscles appearing to be abnormally sensitive to temperature changes.

*Modified Hemoglobin.—*Where there is prolonged hemorrhage or localized hemorrhage in tissues, we are apt to find the hemoglobin extensively modified, a fact which is graphically shown by the successive changes of color of a "black eye;" the substances eventually obtained are **hematoidin, hemosiderin,** and **hemofuscin.** Hematoidin is identical with bilirubin, and is red, iron-free, and to be found in the central part of a large hemorrhage. It is crystalline, in which it differs from hemosiderin, which is always found in the form of amorphous granules. In the anemias, and diseases where there is extensive destruction of red corpuscles, hemosiderin may be deposited extensively in the liver, as happens also in the condition known as **hemochromatosis;** it is an albuminate of iron in which the iron is relatively loosely combined, and hemofuscin probably represents a yet more stable combination of the same sort.

Pseudomelanosis.—This is the dark greenish to black coloration seen postmortem in the liver, the spleen, and the stomach wall, when these organs have lain against the intestine, sulphuretted hydrogen set free therefrom combining with the more or less modified derivatives of

19

hemoglobin and leading to the deposit of sulphide of iron. **Hematoporphyrin** is an iron-free derivative of hematin which is set free in the urine, especially after the use of certain drugs such as sulphonal, whose acid constituent set free in the blood, acts upon free hemoglobin.

Jaundice; Icterus.—The pigment of the constantly secreted bile is derived from the never-ceasing destruction of red corpuscles, which after a short existence of a few weeks fade away in the blood stream or are picked up by the phagocytic cells of the spleen and liver, their hemoglobin, either unaltered or modified, being absorbed by the endothelium of the hepatic capillaries, and by them passed on to the liver cells to be broken up. The iron-free part is discharged into the bile capillaries as bilirubin, the pigment of the bile; as to the iron-containing part of the hemoglobin, it is evidently jealously preserved by the organ, for very little passes into the bile, and relatively little remains stored in a combined state in the liver. Should the bile pigment fail to be discharged from the liver, it accumulates and regurgitates into the blood and lymph vessels, and is carried in a soluble state to the tissues elsewhere, in which it is dissolved, causing them to assume a bile-stained appearance. This staining is **jaundice** or **icterus**; the accompanying symptoms, such as itching of the skin, slowing of the pulse, mental depression, and melancholy (literally *black bile*) are entirely subsidiary, due to associated absorption of bile salts, etc. The blood, the urine, and the tissues show the chemical reaction for bilirubin or the more highly oxidized biliverdin, and the liver is the first organ to show this coloration.

Clinically, the sclerotics of the eye, the mucous membrane of the mouth, and the hard palate show pigmentation early, the skin quickly shows it and the connective tissues throughout the body; cartilage, the cornea, and in general, the nervous tissues (save in infants) are relatively unaffected; the secretions, the urine, the sweat, the saliva show it; the milk more rarely, and the tears (it is said) never; the pale color of the feces indicates that little, if any, is discharged from the glands of the stomach and intestines. The skin may show any gradation between pale yellow and deep olive green, and the disappearance of the color is usually slow.

Etiology.—For the greater part of this generation the accepted teaching has been that true jaundice is always obstructive in nature, with regurgitation of pigment into the circulation. In obstructive jaundice, properly so-called, it is obviously so, for there is an obstruction in the bile channel somewhere between the hepatic lobule and the papilla in the duodenum; there may be congenital narrowing or absence of the main ducts, inflammatory swelling of the walls with narrowing of the lumen (**catarrhal jaundice**), growths or foreign bodies within the passage, new growths outside the passage, pressing upon it, or perhaps even a spasmodic stricture of the duct. With these the bile channels are distended, and it is found that ultimately the pigment injects a fine intracellular network of channels connecting with the bile capillaries.

This network surrounds the nucleus of the cell but does not enter it, and if distended, throws back the bile upon the cell, whence it is at once absorbed by the lymphatics; and perhaps less rapidly, but surely, the pigment makes its way into the hepatic blood; the latter process is much hastened if rupture of bile ducts should occur. A second way in which jaundice can be caused is by the breaking down of a large number of red corpuscles in the circulation; the liver cells, presumably overloaded, excrete a concentrated, inspissated bile by which the fine channels are blocked; the obstruction is not complete, the feces may remain colored, and the jaundice may not be very severe. Such a form of jaundice may occur in sepsis, and is evidently **hemohepatogenous** in its nature. Yet another kind of jaundice is found in such states as acute yellow atrophy of the liver, in phosphorus poisoning, and in the infective jaundice of children where the pigment is evidently freed from liver cells during their destruction. It must be remembered, in fact, that whenever many liver cells are destroyed at the same time jaundice may supervene. Finally, severe shock or nervous disturbance has been followed by jaundice, a phenomenon which we are not able to explain.

Hematogenous Icterus.—Within the last few months it has been clearly demonstrated by Whipple and Hooper that in a dog in which liver only, or liver, spleen and intestines have been cut out of the circulation, bile pigment appears in the urine after the intravenous injection of hemoglobin. It is evident, therefore, contrary to our previous opinions, that there can be a hematogenous origin of bilirubin—a true hematogenous jaundice. Recognizing previously this hematogenous pigmentation we have ascribed it to **urobilin**. These observations suggest that bilirubin may be the cause. The lemon-yellow tinge of the skin in grave anemia and the paler color of cancerous cachexia, as well as the discoloration of the skin in hemochromatosis, appear to be of this order.

Other Endogenous Pigmentations.—**Melanotic Pigmentation.**—Of the autochthonous pigments not derived from hemoglobin, the most important are the melanins, bodies poor in iron but rich in sulphur, which exist normally in the choroid of the eye, in the Malpighian layer of the skin, in the hair, and in the membranes of the brain, and are lacking in so-called Albinos. Increases of pigmentation are seen in pregnancy, in exophthalmic goitre, in certain neurotic states (melasma), in Addison's disease, and in melanotic tumors. This deposit of melanin appears to be due to a process in which oxidases act upon the chromogen group of the protein molecule, with the production of pigmented substances allied to tyrosin and the members of the aromatic series of protein dissociation products; these fail to undergo further conversion and so accumulate in the tissues.

Lipochromes.—These are colored fatty bodies, which give color to the fat, to the corpora lutea, to xanthomas and chloromas, and under certain conditions, to the cells of the nervous system. Present indications are that they are fats combined with tyrosin-like bodies.

Exogenous Pigmentations.—These consist of colored substances absorbed by and deposited in the tissues, or colored derivatives of substances not themselves colored. Tattooing is a familiar example of the first of these, where insoluble particles of vermilion or another pigment are rubbed into fine punctures in the skin. The particles, those at least which are not carried away to the nearest lymph nodes, remain in the outer layer of the corium, whence some of them are gradually removed, producing a fading of the color. A superficial inflammation lasting some time may almost obliterate the tattoo mark, because leucocytes are called to the part and engulf particles of pigment. More important are the pigmentary deposits in the lungs from inhalation, the **pneumonokonioses** (from κόνις, dust). The commonest of these is **anthracosis**, the deposit of coal dust found in the lungs of city dwellers and coal miners. These deposits are black, whereas rather gray in color are the deposits of silicious particles in the lungs of quarrymen, stone-cutters, and workers in granite (**chalicosis**—χάλιξ, a pebble—or **silicosis**). The lungs of knife-grinders, glass-polishers, and others working with iron or iron-oxide dust become a rusty red (**siderosis**); those of pottery workers show dirty white deposits in the lungs (**aluminosis**), and those of workers in tobacco dust a rusty brown deposit (**tabacosis**). It has been shown in Klotz's laboratory that dust particles in the air which are not entangled on the moist wall of the nasal cavity do not appear in the mucosal cells of lower parts of the respiratory tract, but make their way to the pulmonary alveoli, where they are seen in endo-thelium-like cells (which may, per-chance, be the large mononuclear leucocytes). If not discharged in the sputum they may remain in the in-teralveolar septa or may make their way into the lymph stream and so to lymph nodes. Once there, they

Fig 120

From section of an anthracotic lung to show fibrous areas enclosing deposits formed of fine coal-dust particles (high power).

may disintegrate and leave their pigment to the endothelial cells or they may carry it to the nearest lymph node. This explains the deposit so abundantly present in the lymph nodes of the respiratory tract of a city dweller; but it is well to remember that a node that appears absolutely black to the naked eye may under the microscope prove to be a fairly normal structure, the pigment being seen in scattered masses. Wherever such insoluble particles find lodgement they act as mild irritants, giving rise to a development of new con-nective tissue in their neighborhood which may be so localized around

a large collection as to appear like a tubercle; a lung so affected not infrequently falls a victim to actual tuberculosis, the damage being wrought partly, too, by the physical blocking produced in lymph channels.

Of changes induced by bodies that enter the system in a colorless form and give rise to a colored deposit, the best examples are the "**blue line**"
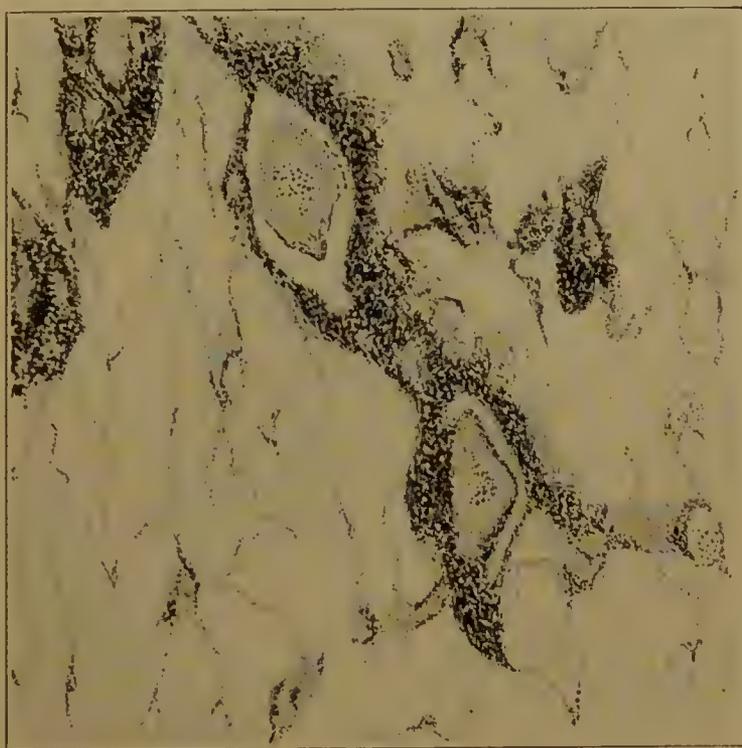
Anthracosis of lung. Note that particles are deposited in interalveolar septa in all parts of the section. (Professor Oskar Klotz.)

of lead poisoning and the deposit of silver in the tissues, known as **argyria**. The "**blue line**" is due to a deposit of lead sulphide in the gums at the edges of the teeth, which is a result of the combination of the soluble salt of lead, circulating in the blood and lymph, with hydrogen sulphide given off from the decaying food material lodged in the interstices between the teeth and the gums. When soluble salts of silver are present in the body fluids they become reduced and metallic silver is deposited in the tissues, especially the connective tissues, becoming visible in the dusky, obscurely silver tint of the skin.

NECROSES

Necrosis is death of cells, of tissues, or of parts composed of many tissues, in spite of which death the organism as a whole continues to live.

Causation.—It has already been shown that there are many gradations of cell disturbance, in some of which quick death of cells or tissues

occurs (**necrosis**) while in others the cells undergo a slow degeneration which terminates in death (**necrobiosis**, better **bionecrosis**). Those forms of necrosis and bionecrosis which occur as a result of degenerative change

FIG. 122

b   a
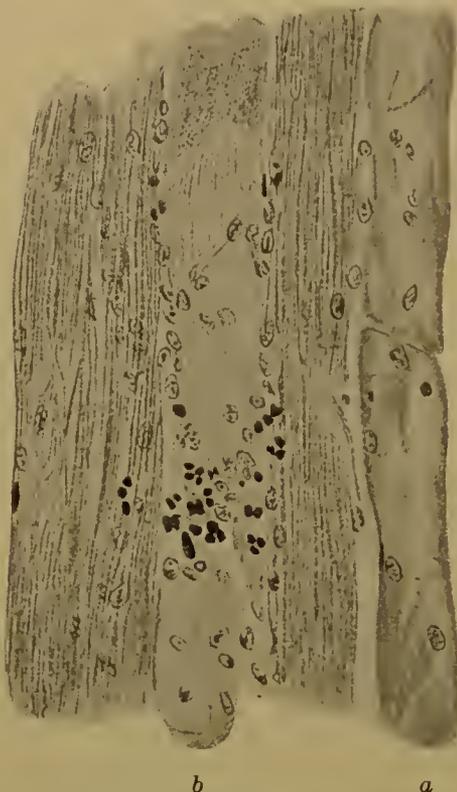
Wax-like degeneration of muscle fibres (*a, b*) seventeen hours after temporary ligation of vessels of the same. In *b* there is already some accumulation of leucocytes. (Oberndörffer.)

FIG. 123
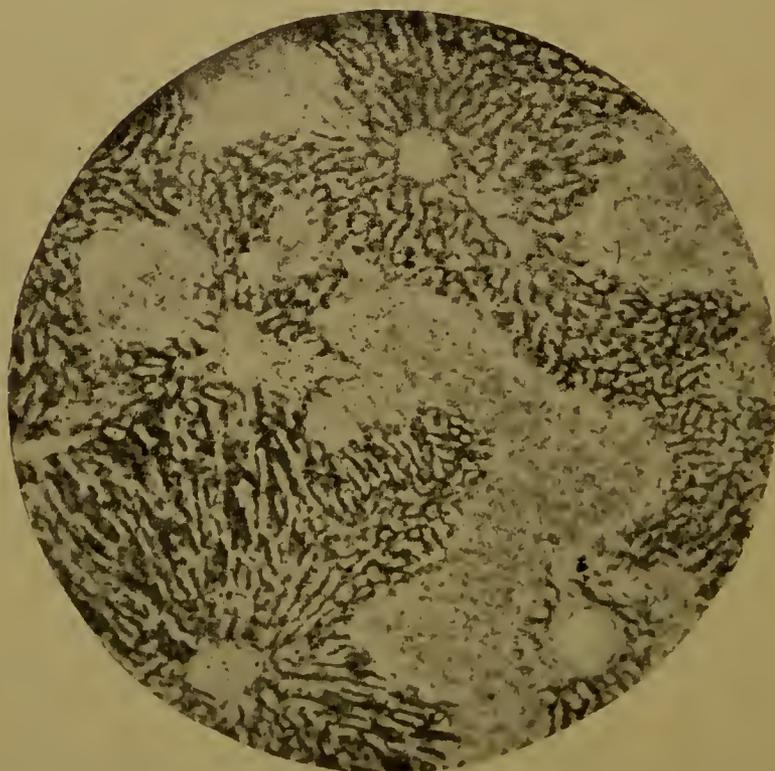
Multiple focal necroses in the liver of a rabbit subjected to experimental glanders. (Duval.)

induced in the cell have been dealt with, but there remain those conditions of necrosis set up by circulatory and nervous disturbances.

Circulatory Disturbances.—Necrosis is induced, on the one hand, by arrest of the blood supply, and, on the other, by deficient or perverted quality of the blood with, as a result, deficient nutrition. In a general way, it may be said that occlusion of the afferent artery and occlusion of the efferent vein of an organ alike produce death of that organ; in both cases there is a lack of oxidation of the tissues, death occurring in those cases in which there is a relatively poor collateral circulation. Necrosis will be caused, as has been said, by ligation of an afferent artery or efferent vein; pressure on the vessel by tumors, cysts, etc.; thrombosis, the coagulation of the blood within a vessel; embolism, the blocking of a vessel by a foreign body in the wide sense of that term; the constricting action of a drug like ergot or disease of the artery wall with proliferation of the intima inducing a partial or total occlusion. If the agent be applied suddenly, necrosis follows; if gradually, bionecrosis.

Inadequate Nutrition.—General malnutrition, tending to a weak heart action and an inadequate blood supply, leads to a progressive state of necrobiosis, to which the different orders of tissues respond differently, the specialized tissues being more readily influenced than the lowly connective tissue.

Nervous Disturbances.—Two questions here arise: can stimuli from the central nervous system set up necrosis? (which is to be answered in the affirmative), and can the loss of nerve supply lead to a like result? (which is to be met by a qualified negation). Central stimuli can apparently affect the vasomotor system so that constriction of the vessels may be followed by local anemia and even by necrosis as in **Raynaud's disease (symmetrical gangrene)**; the loss of nerve supply may lead to cell inanition, but can only predispose to necrosis. A good example of this is seen in the supposition once widely held, that section of the fifth nerve led to ulceration of the cornea, and that neurotrophic keratitis was a definite entity; but we now know that if in these circumstances the cornea be protected from light, dust, and injury, no keratitis occurs. Nevertheless, true though it is that nerve loss is merely a predisposing factor, it is to be admitted that inanition atrophy and gradual death of cells will follow upon loss of nerve connection with consequent inactivity of the part.

Forms of Necrosis.—Distinction, partly clinical, may be made between different forms of necrosis; there are (1) necrosis of individual cells; (2) those affecting small groups of cells, **focal necroses**; (3) those affecting circumscribed areas, as a result of vascular obstruction—infarcts, and (4) necrosis affecting parts rather than local tissues—gangrene.

1. **Necrosis of Individual Cells.**—In addition to the degenerative changes already dealt with, there is the waxy degeneration known as **Zenker's degeneration** of muscle, seen especially well in the recti

muscles of the abdomen in typhoid fever, in muscles after trauma, and at times in the heart muscle. The fibres lose their striation and become waxy or glassy in appearance, the sarcolemma still intact. It appears to be a coagulation of the muscle substance, the myosinogen becoming converted into myosin.

2. **Focal Necroses.**—In cases of severe infections there occur, in various tissues, minute areas of necrosis scarcely visible to the naked eye; such are seen in the lymph follicles in diphtheria and typhoid fever; in the liver in typhoid fever and other forms of sepsis, even chronic forms, and most marked of all in the liver in eclampsia and allied states.

Fig. 124

Waxy degeneration of rectus abdominis in typhoid. (M. B. Schmidt, Path. Anat., Aschoff.)

The causation of these focal necroses is yet unsettled. There is considerable evidence in favor of thrombi, sometimes hyaline, which may be formed by hemolysis of red cells, or by alteration of capillary endothelium which has been killed by toxins and cast off into the lumen.

Fat Necrosis.—Of quite a different causation are the necroses which occur when the fat-splitting ferment present in the pancreatic secretion comes in contact with unprotected tissues. These are opaque, whitish-yellow islands of small size seen in the fatty tissues, generally in the vicinity of the pancreas. Any circumstance which allows the pancreatic secretion to act upon tsisues other than the pancreas or the intestinal wall may lead to their formation.

3. **Infarcts and Coagulation Necrosis.**—The production of infarcts will be more fully considered later, but it is needful to mention here coagulation necrosis, a process best seen in infarcts of the kidney and spleen. In addition to the death of the cells, there is a fibrinous coagulation of the whole area, fibrin being demonstrable; beisdes this, the dim outlines of the tissues of the part, dead and without nuclei, can be seen. The blood fibrin is one of a group of coagulable proteins, and this process is evidently comparable to that which obtains in Zenker's degeneration, where myosinogen is converted into coagulated myosin. Closely allied to this is **colliquative necrosis**, in which there is liquefaction of the dead tissue as a process of self-digestion or autolysis, not to be confounded with **putrefactive necrosis**, where the liquefaction is the result of proteolytic powers of bacteria. The former is seen in infarcts of the brain and in the centres of tumors and large thrombi, especially in the parietal thrombi of the heart cavities.

4. **Gangrene and Mortification.**—The death of large areas may be

brought about by many agents—by vascular obstruction, by acute infection, by burns, frost-bite, corrosives, and physical forces such as

Fig 125
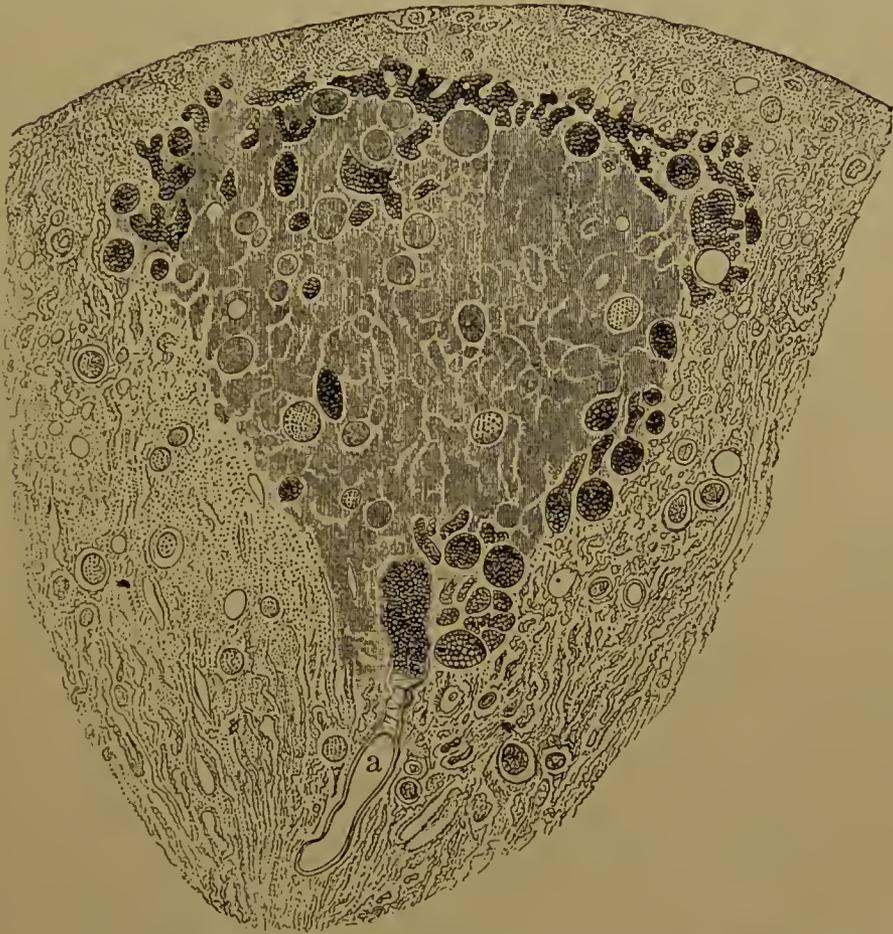
Anemic infarct of cortex of kidney to show coagulation necrosis, with surrounding zone of congestion: *a*, artery.   (Orth.)

Fig. 126
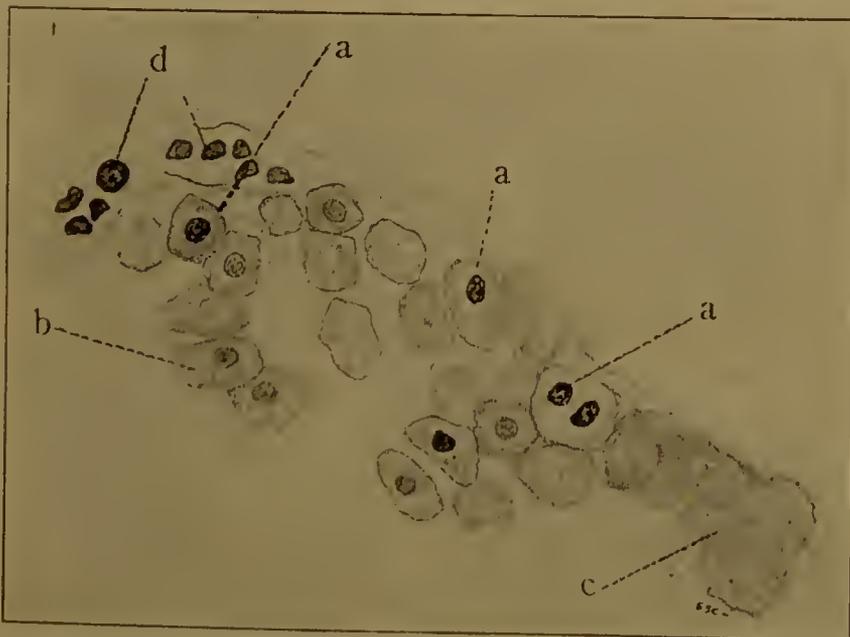
From a section of an adrenal gland, to show the gradations in cell damage leading to coagulation necrosis. *a*, adrenal cells still retaining nuclear stain; *b*, the same with fading of nuclear chromatin; *c*, completely necrosed cells seen as fused shadows; *d*, blood corpuscles.

radium, the x-rays, and electricity. The results of such necrosis vary widely. Where the necrosed area is small, and not infected (1) **absorption** occurs. By autolysis and the activity of leukocytes the dead part may be removed and its place taken by regenerated tissue of the part. More often, especially in areas of larger size, (2) **cicatrization** occurs; surrounding the dead area is a zone of reactive inflammation induced by the presence of the dead tissue and the diffused-out products of its disintegration; from this zone a formation of granulation tissue and vascularization of the same arises. In some areas, as in the brain, where reparative process is comparatively slow by reason of the relatively small amount of supportive tissue, and where colliquative necrosis is prone to occur, instead of a solid cicatrization, there is likely to be (3) **cyst formation.** In tissues such as bone that are so dense that disintegration of dead matter is a long-drawn-out process, the surface portions of the dead area may be disintegrated and loosened from the surrounding tissues, and the central mass, not yet disintegrated, may remain as (4) a **sequestrum,** lying in a cavity and bathed by purulent fluid. Another sequel to colliquative change is (5) **inspissation,** in which the fluid part of the dead material drains away, leaving a gradually thickening residue, which, becoming cheesy in consistence, is prone to be a seat of calcareous deposit.

Coming to the consideration of gangrene, according to the amount of blood entering the dead area and the rate of evaporation of fluid from the surface, occurs (6) **moist gangrene** or **sphacelus,** or (7) **dry gangrene** or **mummification.** In moist gangrene, as in the lung, intestine, or an extremity, blood enters the part and evaporation is prevented, the dead tissue becomes waterlogged, and by the entrance of various microbes putrefaction sets in; the affected tissue is swollen and livid; on the skin large blebs form filled with fluid; the discharge is foul from bacterial growth, and the soft tissues gradually become decomposed and liquefy, the bony portion being the last to yield. Dry gangrene may occur in the extremities and the ears, the necrotic portion becoming shrunken, wrinkled, and dark brownish black in color, like mummy flesh. At the boundary between the living and the dead tissue, a zone of intense inflammation develops, the line of demarcation, at which, by leucocytic and cytolytic activity, a separation and ultimately a detachment may be made.

DEATH

Why does the body die? Apart from any philosophic pronouncements we can find some definite knowledge on the subject. Death is not an inherent quality of living matter; the schizomycete—and this is true of all protozoa—within certain limits of heat and cold, moisture and dryness, grows, divides, and adapts itself to change over long periods of time; accidental death may supervene, by desiccation, by physical and chemical means, but in the processes of such life there is no suggestion

of death. In the hematozoön of malaria, its disappearance is not death, but a division into many new living individuals, and all of the original body save some paraplasmic pigment appears to enter into the new individuals. With the multicellular organism, death appears; the germ cells alone carry on the continuity and the somatic or body cells die. In the germ cells death is not inherent; in the somatic cells, because of their specialization of function, death becomes inherent. If a multicellular organism or a cell republic could be imagined in which all cells arrived at maturity simultaneously, and in which each cell contributed exactly to the needs of others, there would be no need for somatic death. But such an individual does not exist; different orders of cells are required to be mature and active at different times. In the case of man, there are developed in the embryo, organs, such as the yolk sac, which are merely of temporary use. When their purpose is accomplished they atrophy and disappear, and their place is taken by other organs and a new cellular equilibrium has to be established. The heart and kidneys become functional early; the genitalia relatively late, and the latter, too, cease their functional activity before the organism in general. In the cases in which organs supply internal secretions to the blood and to other organs, the disappearance of those organs leaves the blood and those tissues impoverished in one or another direction; if the function of the tissues that have disappeared be assumed vicariously by other tissues, these latter have their reserve of force decreased thereby. By such constant modification there is increasing stress thrown upon the remaining cells until ultimately somatic death of the tissues in general is brought about by the failure of one or other tissue that is absolutely indispensable to life.

In the interaction of tissues, the circulatory, the respiratory, and the nervous systems are indispensable, and cessation of the activity of any one of them will bring about somatic death; organs, too, at first sight insignificant, such as adrenals or parathyroids, have been proved to be of prime importance. With so many organs, essential to life, it is clear that there may be many different ways in which somatic death may supervene, because the exhaustion of one single system or organ will be enough to permit somatic death to occur. Somatic death, when it does occur, is a cessation of function of these three vital systems, followed by the disintegration and decomposition of the body in general. There is not necessarily immediate death of individual cells. Signs of this somatic death are the cessation of respiration, and of the heart beat, clouding of the cornea, the development of **rigor mortis**, and, finally, of gross decomposition and putrefaction. Rigor mortis is due to coagulation of myosinogen forming myosin, the coagulation being brought about by the lactic acid of the muscle; the passing off of rigor mortis is due to autolytic change; its onset is rapid in those engaged in violent muscular effort at the moment of death and in cases of tetanus or strychnine poisoning; whereas in cases with prolonged wasting or of asphyxia or hemorrhage it may be delayed for a considerable period.

The onset, too, of decomposition is variable in time according to temperature; the normally moist parts such as the intestine show the change quickly. The bodies of those dead of acute infection and of bacteriemia change rapidly not only because the bacteria are present but also because the protective substances that inhibit bacterial growth have been exhausted.

CHAPTER VI

PROGRESSIVE TISSUE CHANGES

OVERGROWTH

Overgrowth of a tissue in which the individual elements preserve their physiological relationship and functions may be shown by an increase in size of the individual element — **hypertrophy** — or by an increase in number—**hyperplasia**[1]—or by both together. **Pseudohypertrophy** is something entirely distinct; here exists an actual atrophy of the individual elements, with replacement in excess by another tissue (Fig. 127). In the so-called "pseudohypertrophic paralysis" the increase in size of the muscle is due to an excessive interstitial develop-

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[1] Some prefer to call these *simple* and *numerical* hyperplasia respectively, which is more accurate but less widely used.

ment of fat cells, while the muscle fibres are degenerated, and diminished in size and in number. It must be understood that hypertrophy and hyperplasia should be referred to only in connection with the specific elements of the organ concerned—the liver cells in the liver, the muscle cell in the muscle (anatomically defined) and so on. Hypertrophy, itself, is a misleading term; etymologically it means "overnutrition," but scientifically it means nothing of the sort; the term is so widely used in its generally accepted sense that it would be inadvisable for us to employ it otherwise.

FIG. 127
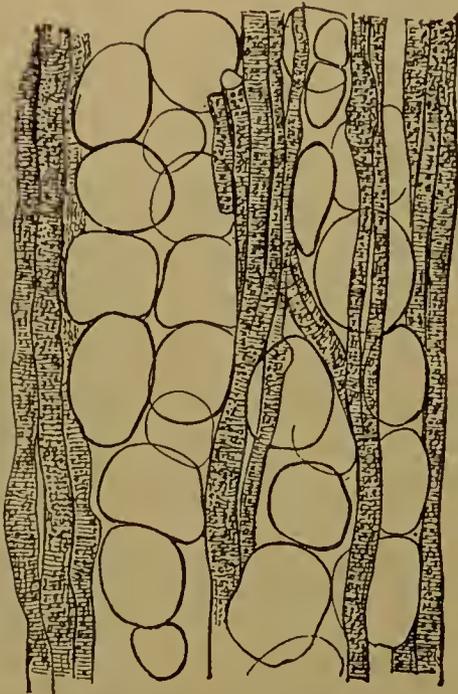
Longitudinal section through muscle of calf of leg in pseudohypertrophic paralysis. The muscle fibres exhibit atrophy; the increase in bulk is due to the excessive development of fat cells. (Orth.)

Kinds of Overgrowth. — 1. **Physiological Hypertrophy.**—The type of this is the pregnant uterus, which enlarges by hypertrophy and hyperplasia. The total size in cubic content, of the hypertrophied muscle, is many times in excess of the normal; a great increase in blood supply also occurs, and muscular contraction begins from an early period of pregnancy. Increased nutrition cannot be said to be the chief cause of this overgrowth, because the presence of a fibroid in the uterus for example, unaccompanied by any marked increase in vascularity, may be associated with great hypertrophy. The excessive development of muscles by exercise, as in the blacksmith's arm, is certainly due partly to activity, but with increased nutrition, because a muscle during exercise obtains an increased circulation through it. Muscle is not the only tissue that undergoes growth as a result of increased function (plus nutrition), because the bone shows like capacity, becoming thickened, in those of active athletic habits, along the ridges and over the tuberosities where muscles are attached, the increased stress inducing increased growth.

2. **Adaptive Hypertrophy.**—Largely the result of functional activity, are the hypertrophies of hollow viscera following upon an obstruction to outflow. Such are the overgrowths of the heart or bladder in which, just as in the uterus, the fibres become larger than normal; the normal heart weight is 250 to 300 grams, and the hypertrophied heart has been known to reach nearly 2000 grams in weight. The overgrowth occurs relatively more readily in a young person than in an elderly one. A parallel case is the hypertrophy of the media of an artery where there is an habitually heightened blood pressure, in which case the increased work is of the nature of stress. This adaptive hypertrophy is some-

times called **compensatory**, a term which ought to be restricted to the form of overgrowth with which we are about to deal.

3. **Compensatory Overgrowth.**—This is overgrowth to make up for loss of tissue, as where one of a pair of organs is removed or destroyed; the other may grow to the size of the original pair. It may be stated that in all the paired organs of the body, one is capable of doing the work of both, and in performing it, hypertrophy ensues, but the statement ought to be modified slightly, because the perfection of the compensation and its extent vary with the age of the tissues, the younger they are the more complete being the compensation. At this point, it is of service to point out wherein these cases are examples of true overgrowth, and not of regeneration; in a case such as that in which a part of the kidney is removed, there is not a new formation of units, *e. g.*, tubules, but a growth in length, size, and the number of their cells in those that have remained undestroyed. Similarly, the hypertrophying liver does not produce new lobules, but only new cells. It might be said that the production of new cells is itself a regeneration, strictly speaking, but we think it needful to apply the term only to those examples in which a cell complex is budded off from an already existent mass of cells.

4. **Vicarious Overgrowth.**—This is the condition in which one organ fails through disease or destruction, and organs of another order, apparently of allied function, undertake the work, and overgrow as a result of the extra call made upon their resources. The pituitary gland is thus the site of vicarious overgrowth when the thyroid is atrophied or removed; it is said, too, that Brunner's glands in the duodenum have a similar relation to the pancreas. The bone marrow and the hemolymph glands appear to be able to perform the work of the spleen.

5. **Irritative Overgrowth.**—It is a familiar observation that in cases of inflammation there is an irritative stimulation of the supportive tissues to replace destroyed parenchyma. There is evidence to show that a productive overgrowth of supportive tissues may occur not secondarily to inflammation, but primarily; examples are found in the increased growth of bone when phosphorus is given in minute doses; the distinction between this and real inflammatory overgrowth is, we admit, unimportant.

6. **Nutritional Hypertrophy.**—When a weak toxin stimulates cells to overgrowth, it is possible that it does so by increasing the absorption and assimilation of which the biophoric molecule is capable. Even if such be the case, we must yet continue to include those cases among irritative overgrowth, for we are not yet certain that there is such a thing as nutritional hypertrophy, pure and simple. Mere hyperemia, due to increased arterial blood passing to a part is occasionally found to lead to hypertrophy; but even here the cells must be called into increased activity (as by the increased warmth of the part) before they can utilize the excess of nutrition that is around them. There is experimental evidence that increased temperature of a part stimulates growth;

a rabbit's ear, kept warm, becomes of a greater size than its fellow which has been kept at a normal temperature. What then will call cells into the required activity? Many stimuli are able to do this, and some of these relatively slight ones, such as the constitution of the fluid that bathes the cell with reference to its oxygen and carbon dioxide content, to say nothing of the external nervous and other stimuli which we are more accustomed to bear in mind.

There must be included in this group the hypertrophies occurring in myxœdema and acromegaly, diseases which arise in persons whose internal secretions are disturbed; myxœdema arises when the thyroid secretion is deficient or absent, and exhibits an excess of interstitial mucin in the tissues, and subsequently a real overgrowth of the supportive tissues. Similarly, acromegaly is an overgrowth of the bones of the head and the extremities, associated with disease of the pituitary body. These are evidently cases of nutritional overgrowth, which are instituted by some stimulus, ordinarily held in check by an internal secretion and possibly of a chemical nature. Not far removed from this, is the form of overgrowth which is called sympathetic, such as the overgrowth of breast tissue in pregnancy; this would be frankly classed among the physiological overgrowths, save for the fact that it is due to something of the nature of a hormone, as shown by the enlargement of the breast that occurs in the non-pregnant animal inoculated with an extract of fœtal tissue or corpus luteum.

During the consideration of nutritional overgrowth, we must not lose sight of the fact that abundant nourishment is most effective when coupled with some activity, but that occasionally the stimulus to activity is given by the increased nutrition itself; this, however, is not to be depended upon, and generally the opposite is true, that the activity of function must precede the overgrowth; this activity, too, must not be excessive or the result will be not overgrowth, but the contrary, atrophy.

Simulated Overgrowth.—Sometimes we seem to see examples of excessive overgrowth, which are not really such; an example is seen in the occasional enormous development of certain teeth in animals. These teeth, ordinary opposed to other teeth, are by attrition kept to a certain size; if the opposing tooth be lost, the result may be an enormous growth, which, however, speaking strictly, is not a real hypertrophy, but merely an absence of the normal wearing away.

REGENERATION

Loss of substance, not so great nor affecting so vital a part as to cause death, is remedied by regeneration of the lost part or by compensatory overgrowth and increase in the functions of other parts. Speaking generally, one finds that regeneration is slight in higher forms, and indeed it is safe to say that among the lower and simpler forms of

life the capacity for regeneration is the greatest and most complete. The illustrations of this statement are familiar, and need not be reiterated. The hydra and allied forms will regenerate in any direction in which the opposing cells have been removed, but this within limits, for **geotropism** is a factor. In a tubularian the head will grow only upon the upper end, the foot only upon the lower end. This is valuable as indicating the power of influences external to the body, and shows us that the capacity of the cell to proliferate is a function of its relation to other cells, and of the action upon it of certain physical influences. We say its relation to other cells; for it has been noted that the planarian (a flat worm) head undergoes perfect regeneration only when the ventral nerve ganglion has not been destroyed. A parallel instance is seen in some crustaceans, where, if an eye be removed, there develops in its place not a new eye but an antenna-like organ, unless the ganglion cells connected with the eye have been left intact, in which case an eye is redeveloped. Thus it seems that while nerve cells do not initiate the regenerative process, they yet influence, or even control the ultimate cell relationships and functions. Nor is it the active functioning of the cells that initiates the regenerative process, for in the earliest stages of a regenerating eye or limb of an arthropod, the new parts are entirely incapable of function.

In the higher vertebrates and in man, the capacity to reproduce lost parts and organs is wholly wanting. We can, however, recognize the capacity to reproduce lost *tissues*, but this only within certain limits.

1. *If an organ be completely removed or destroyed, it cannot regenerate.* If only a part be taken, the rest may proliferate and bring about regeneration; if a whole bone be removed, it is not replaced, but if the periosteum be left, a regeneration may occur.

2. *The higher and more specialized the tissue, the less is its capacity for regeneration.* A part of a nerve cell or a fibre may grow again after destruction but not the whole neurone.

The muscles regenerate, but imperfectly. Nor is it remarkable that regeneration in the higher kinds of tissue should be a difficult matter, because not one, but several, orders of cell develop side by side, and the more rapidly developing new-formed connective tissue, for example, is apt to bring pressure to bear upon the new acini, or lobules, and to cause their atrophy. The salivary glands and the thyroid regenerate moderately well by a process of budding from the ducts, but most of the other complex organs and glands can scarcely be said to regenerate.

In the liver it is to be noted that the part most ready to proliferate is the bile duct, and this is quite in accordance with our knowledge, for we find that where different cells of the same order are differentiated to varying degrees of perfection, the less differentiated are more apt to regenerate than the more differentiated; in an ordinary gland, for example, the cells in the neck or in the duct are more likely to proliferate than those of the acinus. Nevertheless the liver cells proper have not wholly lost the power of regeneration; after experimental

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necrosis of the centres of the lobules the dead cells are replaced by others originating from the cells of the middle zone.

3. Tubules in the kidney, and lobules in the liver of the adult regenerate only to the extent that lost cells are replaced. Only in the very young are there indications that new tubules or lobules may be formed. *Regeneration is the more complete the younger the animal.*

There has been a good deal of discussion as to why regenerated tissues so often atrophy in a comparatively short space of time. The reason is, probably, that where tissues of widely different degree of differentiation exist side by side in the same organ, the less differentiated gain so great a lead over the more differentiated and regenerate so much more rapidly that active pressure is brought to bear upon the latter to their detriment.

Regeneration of the Various Tissues in Man.—Connective Tissue.— *White Fibrous Connective Tissue.*—This is the most active of all regenerating tissues in the body. The fibrous connective-tissue cell, under stimulus, swells, becomes larger, gains more cytoplasm, and gives off a rather round, plump, soft cell, which shortly becomes somewhat more fusiform—the fibroblast. There has been considerable discussion as to the derivation of this cell, and there seems no reason to doubt that it arises alike from the endothelium of the vascular channel and the supportive connective tissue, two kinds of tissue whose close similarity, even whose absolute identity we have previously upheld. Going farther, many hold that the plasma cell also takes part in regeneration.

There are several different cells found wandering in the tissues, which Maximow includes under the term **polyblast**, and following his observations, there is an increasing tendency to believe that all such cells, having a round or oval nucleus, as distinguished from those having a partite nucleus (polynuclears and eosinophiles) may take part in tissue upbuilding.

Elastic Connective Tissue.—There is no doubt that elastic tissue regenerates. It is to be found, newborn, in areas of new connective tissue, and in such places as the intima of arteries; but we have not yet settled what kind of tissue gives rise to it, nor do we think it likely that its origin is different from that of the white connective-tissue fibre. It is to be kept in mind that elastin, the component of the elastic-tissue fibre, is a relatively inert protein differing but slightly from the more active albumins of the supportive cell.

Fatty Tissue. — It is uncertain whether we should speak of the regeneration of fatty tissue, because we are not yet certain if fatty tissue is a distinct entity or is a modification of connective tissue; there is much evidence in favor of the belief that it is not a distinct tissue. What is the fat cell? Some, like Mallory, regard it as a particular type of cell, distinct from the connective-tissue cell, and that because there are connective-tissue areas, such as the portal sheaths in the liver and the vascular sheaths in the brain, in which under no circumstances do fat cells show themselves. It is chiefly considered to be a connective-

tissue cell, or a number of connective-tissue cells, which have multiplied in the neighborhood of a capillary; in the cytoplasm of such cells fat droplets appear, fuse, and push the nucleus to one side, until we see, histologically, the huge fat droplet, surrounded by the cell membrane, which shows at some part of its circumference the flattened nucleus, representing the seal in a signet ring looked at from the broad side. Some say that this large cell arises by fusion of smaller cells, and in places where the fat is disappearing one can sometimes see a number of closely aggregated cells. In view of the difficulty of settling this primary question of the existence of the true fat cell as an entity it would be wrong to make any statement stronger than this, that, at the present time, evidence of the regeneration of fatty tissue in any way comparable to the regeneration of the tissues we have dealt with, is wanting.

Cartilage.—Cartilage has the power of regeneration, although its growth is slow. This occurs in two ways, distinct one from the other: (1) perichondrial regeneration, and (2) regeneration direct from the cartilage.

In the former the perichondrium is swollen and broken away from the cartilage, and the space between perichondrium and cartilage is filled with fibrin. A great multiplication of cells is seen on the inner aspect of the perichondrium, and these cells, which look like ordinary connective-tissue cells, come to replace the fibrin. The oldest, which are farthest from the perichondrium, become rounded, or polygonal, and lie in a transparent matrix; this obviously is new cartilage. Sometimes, however, the matrix is not transparent, but entirely fibrillar, the fibrils originating from previous cartilage. Between these fibrils are seen cartilage cells, which at first are uncapsulated and single, but later develop a capsule, and become multiple; the fibrils, too, in time disappear, leaving the ordinary cartilage matrix. In the second method, the cartilage proper, when about to regenerate, undergoes a softening of the matrix, and division of the cells, so that a single cartilage cell becomes a group of daughter cells, which group seems to be responsible for the subsequent formation of new hyaline matrix around it.

Bone.—Clinically, the regeneration of bone is an extremely important matter, and it is well to appreciate that the regeneration of bone, like the regeneration of cartilage, is merely the regeneration of a somewhat modified connective tissue. The new cells in each are, in the earliest stages, exactly like the fibroblast. This is not remarkable, when we remember the relationship between the three tissues; cartilage becomes converted into bone, and periosteum may give rise to fibrous tissues, as happens when a fibrous union occurs instead of an osseous. Further, although we are accustomed to speak of bone arising with, and without, the previous interposition of cartilage, both kinds of bone are actually modified connective tissue, and no distinction is to be made in their forms of regeneration. Regeneration of the medulla is of the same order as that of the periosteum. The long bones have remarkable

qualities of regeneration, not only in the periosteum, but also in the medulla, and even in the lamellæ of the bone itself. The lamellæ are constantly being renewed, the old tissue being taken up by the osteoclasts, and the new bone being laid down in its place, so that the position of a lamella is constantly being shifted. In addition, there is a constant deposit from the periosteum, as well as the medullary cavity during the entire process of growth; all these forces which are thus seen to build up the bone in the first place, take part in regeneration after injury or destruction.

Periosteal Regeneration.[1]—Areas of bone denuded of their periosteum have been seen to obtain a new layer by continuity from the adjacent periosteum; mere stripping of the periosteum from the bone does not necessarily render the bone liable to necrosis. When periosteum regenerates, it arises firmly attached to the bone, and separated from the overlying connective tissue; the direction of the fibres, too, suggests that the growth is from the periphery of the area destroyed.

The Regeneration of Medulla.—Injury to the marrow cells is quickly followed by the usual degenerative changes, which quickly give place to mitosis and proliferation; equally readily the connective tissue around the capillaries begins its proliferation at the margin of the injury, whence fibroblasts are pushed into the injured area. It is remarkable, however, that there is little migration of leukocytes; new capillaries form and a new fibrillar network pervades the area of injury, in the meshes of which are the constantly increasing young marrow cells. Pieces of injured bone are seen surrounded by osteoclastic giant cells.

The Healing of Fractures.—It is scarcely necessary to deal here with the mode of repair in bone because this is so fully considered in works upon surgery, but it may be noted that considerable variation in the process occurs, depending on whether the apposition is good, and the nutrition of both fragments preserved. The more perfect the apposition, the quicker is the repair; the greater the amount of riding of one fragment upon the other, the greater the irritation, the exudation and the callus. A poor blood supply will mean a delayed or arrested union. The callus forms as follows:

(*a*) Hemorrhage and exudation around the fracture, with coagulation.

(*b*) Invasion of the coagulum by cells—polynuclear from the surrounding soft tissues, fibroblastic from the periosteum and marrow.

(*c*) Absorption of the fibrin and replacement of the clot by tissue from the periosteum and medulla, which

(*d*) Becomes converted into cartilage, a step that may be lacking if the callus is small.

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[1] MacEwen and others have of late denied that the periosteum plays any part in the regeneration or even in the growth of bone. We are not as yet prepared to accept those views, holding the opinion that these observers have dealt only with the outer fibrous layer, and not with what may be termed the "cambium" or mother-cell layer in immediate contact with the actual bone.

(*e*) Then begins the process of laying down the osteoid tissue with deposit of calcareous salts in the matrix, either with or without the preliminary intervention of cartilage, the subsequent absorption of the same and its replacement by lamellar bone. In the lapse of time, the excess of bone is removed, and the callus remains just sufficiently strong to secure stability of the part.

Regeneration of Lymphoid Tissue.—The specific cell of lymphoid tissue is the lymphocyte, which is constantly regenerating, and the supportive structure is made up of the comparatively unspecialized reticulum, which we have indicated as the most readily proliferated of all tissues. New lymph nodes appear in various sites in the sub-peritoneal tissue where they have not been previously recognizable; this is doubtless due to lymphocytes coming to rest in areas suitable, as regards food supply, to their proliferation, or perhaps to a sudden accession of growth on the part of lymphatic tissue that has been hitherto latent.

Leukocytes.—Our ideas of the leukocytes tend to the supposition that they cannot regenerate; they arise in bone marrow from the myelocyte, but are unable themselves to institute any process of reproduction, and their appearance in numbers apparently greater than usual in the blood, is not always or necessarily due to increased reproduction, but may be due to a different distribution of leukocytes already in existence. The production of new leukocytes is a process that goes on constantly throughout life under physiological stimuli, and thus can scarcely be properly included among pathological regenerations. It is nevertheless deserving of note that as stated later in connection with the erythrocytes, occasionally the spleen is seen to revert to its embryonic function of developing myeloblasts and so of giving origin to granular leukocytes.

Regeneration of Blood-vascular Tissue.—In the embryo there are two methods by which new vascular tissue can arise: (1) an intracellular formation of blood channels, by which cells hollow out and give rise in their interior to blood corpuscles, the spaces later becoming connected; (2) a process of budding, in which certain endothelial cells of capillary walls give off long protoplasmic processes, without nuclei, which connect one capillary with another; these processes hollow out, and blood passes into and through the process; ultimately mitosis of the original endothelial cell occurs, and the new nucleus passes into the wall of the tube, which places the cells of the new vessel on an equality with the old. In regeneration of tissue, the second method is the one found, and it has been already described in the process of vascularization of granulation tissue (see p. 134).

Regeneration of the Mother Cells of Red-blood Corpuscles.—The red-blood corpuscles arise from nucleated, hemoglobin-containing cells in the bone marrow, the **hematoblasts.** Whether these hematoblasts are able to arise from preformed hematoblasts—a true regeneration— is doubtful; it is more likely that, under the stimulus of necessity,

there may be an increased production of hematoblasts from less differentiated "mother cells" in the marrow; as again, more rarely, in the spleen and, it may be, the lymph or hemolymph nodes.

Regeneration of Epithelium.—Epithelium can regenerate, and new epithelium arises only from pre-existent epithelium. The apparent exception in which epithelium appears in the midst of granulation tissue is explicable by accidental transplantation of epithelium, or by the persistence of epithelial elements deep down, as in the depths of a hair follicle. Another apparent exception occurs in gliomata—new growths arising from the supportive tissue of the nervous system—in which cysts come to be lined by a regular layer of rather columnar cells; it is not certain that this is true epithelium, for one searches in vain for a basement membrane, the cells lying closely upon the less modified individuals of the next layer. Were it proved, however, to be true epithelium, it would not prove the origin of cells of one order from forebears of another order, for the glia is of epiblastic origin.

The epithelium, like the endothelium of bloodvessels and serous cavities, can regenerate completely. If the epithelium of the skin be broken, the lower layers (not the keratinized cells, which are inert, because degenerated) become active, and these cells, becoming elongated, slide over one another, still preserving protoplasmic connection, until they form a somewhat flat skin over the denuded surface, the new skin forming at the expense of the old, which can be seen to be thinner than normal at the edge of the injury. Mitosis quickly begins in these flattened cells. There is as yet no basement membrane, but this is soon supplied, evidently by the fusion of fibrils from the underlying connective tissue. Until this forms there is free passage of leukocytes through the superficial cells, and even phagocytosis of leukocytes by the epithelium.

Fig. 128

"Pseudo-epithelium," or secondary epithelium without basement membrane lining a cyst in a glioma, formed by modification of the superficial layer of glioma cells. (Saxer.)

Hairs, sweat and sebaceous glands may grow again if their deeper parts have not been destroyed, and it is interesting to note that in such cases there is sometimes a downward growth of the superficial epithelium to meet them, an observation that suggests that tissues of the same nature have a reciprocal attraction for one another. If the root bed of the hair be destroyed there is no regeneration; and the same is true of the nail bed in the fingers, although this extends back farther than is commonly supposed, and a portion

of it being left accounts for the appearance of a nail after a terminal phalanx has been removed. This can scarcely account for the appearance of a new nail—or an attempt at such—when two phalanges have been removed. Here we are compelled to admit that it seems as if new conditions had stimulated a metaplasia—a change of nature of cells—of the ordinary skin to a nail-producing matrix. But in general "scar skin" is characterized by complete absence of hairs, sebaceous and sudoriparous glands; epithelium regenerates but not true skin as a whole.

Regeneration of Mucous Membrane.—The process described for the epidermis is found to exist in the mucous membranes, to the extent that cells at the edge of an ulcerated area may lose their cilia, become rounded and ultimately flattened to cover the denuded surface, and even simple gland follicles, like those of Lieberkühn, are reproduced.

The extensive regeneration necessary in the uterus after menstruation, and over the placental site after parturition, is said to be assisted by the persistence of the remains of the deeper portions of mucous glands.

Regeneration of Endothelium.—In a way similar to that seen in epithelium, endothelium by a method of translation and proliferation quickly covers over a denuded area; even fibrin or the cells of a new growth transplanted in the peritoneum may be covered by it. The view usually accepted is that the new covering arises from pre-existing superficial endothelium, but considering the close relation existing between endothelial cells and fibroblasts and connective tissue, it is not impossible that endothelium of such a denuded area may arise from the underlying connective tissue, especially as endothelium has been seen to give rise to underlying new connective tissue.

Regeneration of Glands.—In general, glands undergo but little regeneration. The glands of the simplest structure, such as the Lieberkühnian follicles of the intestine, the uterine and salivary glands, do present instances of the process; in more complex glands the ducts are mainly or entirely the source of new tubules, yet with the modification previously noted, that such regenerated glands have a great tendency to atrophy by reason of the accompanying more rapid and abundant regeneration of the supportive structures which compress them.

Liver.—Where, as in poisoning an animal in the laboratory by chloroform, there is induced a state of necrosis of the liver cells of the centre of a lobule, regeneration occurs by proliferation with simplification of the more peripheral cells, and these new cells with subsequent growth come to occupy the spaces from which the cells have disappeared, so that in the course of a few weeks there may be complete regeneration. So also, where complete lobules have undergone necrosis from one or other cause, there has been observed the formation of new buds or branches from the bile ducts, which, advancing into the framework of the destroyed parenchyma, give origin to new liver cells. Where, however, there has been complete destruction or removal of an area of the liver, the destroyed portion is not regenerated; at most, the remaining liver tissue exhibits some hypertrophy.

Kidney.—A tubule partly denuded of epithelium may be reclothed by the cells still left in that tubule, but no new tubules are developed. Attempts at the formation of a new tubule invariably stop short of the construction of a new glomerulus, so that such a tubule remains imperfect and without function. But in young animals, not in the injured, but in the opposite kidney, new glomeruli and tubules appear to arise, because the kidney is found to contain more than the normal number, and groups of cells near the cortex are considered to be the *anlagen* of new glomeruli.

Fig. 129
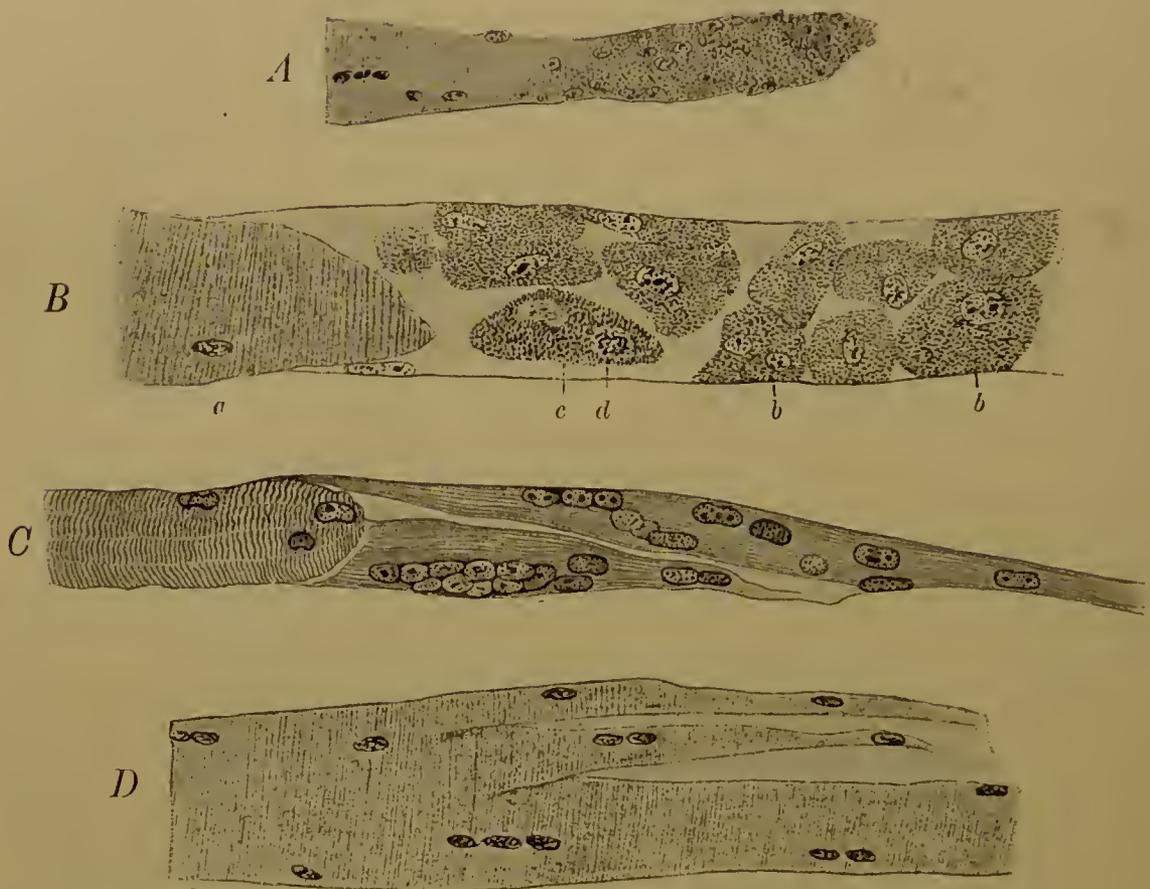
Successive stages in the regeneration of voluntary muscle: *A*, formation of bud of cytoplasm with loss of striation and multiplication of muscle nuclei; *B*, the nuclei acquire cytoplasmic territories and cells, uninucleate and multinucleate, separate from the bud (sarcoblasts); *a*, unaltered end of muscle fibre; *b*, sarcoblasts; *c*, multinuclear sarcoblasts, one nucleus at *d* showing mitosis; *C*, early stage of new muscle fibre, multinucleate and exhibiting longitudinal striation, becoming fused with the original fibre; *D*, regeneration complete but irregular, the original fibre being continued into three processes. (After Volkmann.)

Thyroid.—A certain amount of regeneration occurs in the thyroid, chiefly by a process of budding and separation of new follicles from the old.

Pancreas, Spleen, Testis, Ovary.—In these organs, evidence is in favor of the view that regeneration does not take place.

Muscle.—**Plain Muscle.**—In the stomach, the muscularis mucosæ and the uterus, abundant mitoses may occur after injury, and in some animals, new fibres have been seen to form.

Striated Muscle.—If the substance of a muscle fibre be partly destroyed, but the sarcolemma sheath left, a complete regeneration may occur; but where there is actual injury wrought to the fibres, these contract away from one another, and the regeneration of the interfibrillar connective tissue tends to check the regeneration of the injured muscle. Yet in any given case some fibres will succeed in preserving the sarcolemma and others not. When it is preserved, some nuclei still remain with cytoplasm around them, and these gradually multiply and are surrounded by constantly increasing cytoplasm, lying aggregated in clumps; from such a clump individual mono- or multinuclear cells separate themselves, and absorbing the remains of the old striated substance, they attach themselves to one another or to the undamaged part of the muscle, and gradually become first longitudinally then transversely striated; the old sarcolemma sheath becomes absorbed and a new one appears. When the sarcolemma is ruptured, as in a cut or a laceration, the capillaries are also ruptured and the picture becomes more confused. The ruptured fibres contract into clumps, as before losing their striation, of which the nuclei undergo rapid division, until a chain of many nuclei results; the nuclei tend to collect in the unstriated clumped end of the fibre, where they form terminal "buds"; similar buds may appear laterally on the fibre; these buds elongate, the number of nuclei becomes reduced, the cytoplasm increases, and transverse striations begin to appear.

Regeneration of Nerve Tissues.—**Neuroglia.**—The neuroglial tissue is peculiar in that it is a connective tissue and yet is of epiblastic origin, being in fact so closely related to nerve tissue that at an early stage of development one cannot tell which cells will become nerve-cell bodies and which glia. Even in the adult there is no doubt that glial cells regenerate, and they are able to form not only tumors but replacement gliosis in the case of loss of nerve cells. Some observers have thought they have seen them giving rise to cells which take the function of nerve cells, but this can be determined only in the very young and even then seems to offer ground for doubt.

Nerve Cells.—It may be definitely stated that the nerve-cell body does not regenerate in either man or the higher animals. Mitoses have been seen, it is true, but it is not proved that cell division follows them.

Peripheral Nerves (*Nerve Fibres*).—It may be definitely laid down that any new development of the axis cylinder always originates from a pre-existing axis cylinder, and then only when in connection with a nerve-cell body.

If a nerve fibre or its axis cylinder be severed there is degeneration —the so-called **Wallerian degeneration**—distalward throughout the entire axis cylinder, and on the proximal side, as far as the next node of Ranvier or even higher. We may recall here, also, that as the result of section of a nerve the function of the nerve-cell body is apt to be discontinued, and gradually there may show itself a disuse atrophy

of the nerve-cell body, and the proximal portion of the axone. Regeneration may occur in the distal part of a divided nerve, provided (1) that the parent cell be intact and undamaged; (2) that the organ or part innervated is not atrophied or degenerated, and (3) that a cicatrix does not block the track of the regenerating fibres. With regard to the third of these conditions an imperfect regeneration may in these cases show itself, such as is seen in the so-called **amputation neuroma,** which may form at the end of a divided nerve, in which the growing nerve fibrils become twisted through the fibrous connective-tissue overgrowth of the peri- and endoneurium.

It will be realized that regeneration is most complete when the sheaths of Schwann are intact; this is exactly parallel to the condition seen in the muscle, the neurilemma and the sarcolemma being both very near to the specific nuclei of the myelin sheath and the muscle, the nuclei in fact lying and multiplying close underneath the sheath.

If a fibre be injured the axis cylinder stains imperfectly, becomes fibrillated and disintegrated. The myelin sheath divides up into irregular masses. Now the nuclei of the sheath of Schwann begin to proliferate; they pass between the masses of myelin and pick up from it their cytoplasm. Some of these new cells degenerate and die, and others become elongated and spindle-shaped, and give rise to the new sheath of Schwann and the myelin. The axis cylinder meantime prolongates from the central end of the damaged nerve and has at its tip a nodular mass of protoplasm, which is apparently motile and creeps ahead, laying down the axis cylinder like a telegraph line behind it, its general course being along the lines of the old sheaths of Schwann.

Regeneration after Section.—Regeneration under these circumstances is brought about in the same way, but the new spindle-shaped cells and the new end of the axis cylinder being no longer guided by a remnant of the original sheath may take a tortuous course, especially if the two ends of the nerve are widely apart. Time is lost in the process on this account and quicker regeneration is obtained if a guide of some sort be placed between the two ends; such a guide may be a hollow piece of bone or a bundle of catgut threads. In spite of a considerable distance between the two ends and the piling up of scar tissue as an obstacle very remarkable regeneration of peripheral nerves has occurred, gaps of 10 and 12 cm. in the dog having been bridged, the process requiring a couple of years.

GRAFTING OR TRANSPLANTATION

Transplantation means the inserting of living tissue into living tissues and may be *autoplastic,* that is, when individuals' own tissues are grafted on themselves, *isoplastic,* where the tissue of another animal of the same species is used, or *heteroplastic,* with tissues of another species.

Implantation, while a similar process, does not demand the use of a living tissue as a graft.

The remarkable results obtained by grafting in arboriculture and gardening are familiar, and low forms of animals show a great readiness for growth if they are grafted, and that with tissues or parts of another species of the same genus; with the warm-blooded animals, however, this is by no means the case. One may make a general statement to the effect that immediately after grafting the tissue inserted may grow, yet in a comparatively short time the planted tissue becomes absorbed and a cicatrix alone may remain, although sometimes the graft forms a framework upon which the regenerated tissue fills in the area. Even in this short period of growth after transplantation it is often notable that the proliferation of the transplanted tissue occurs through generations of cells that gradually become less and less specific. Expressed in other words, there is at once a reversion in the type of the cells transplanted. Considering this fact one would naturally conclude that if embryonic vegetative tissues were taken in the first place, transplantation would be much more likely to succeed, and such is the case. But even in these cases, as where portions of chick embryos are transplanted to chickens, the graft in a few weeks begins to show signs of becoming absorbed. In this connection the reader may recall that John Hunter transplanted a cock's spur to its comb, with the result that at first the spur grew to large dimensions, but with an inevitable tendency to atrophy and subsequently fall off.

When we note the results of transplantation of the **thyroid** we see rather more successful examples. It is now a good many years since the cat's thyroid was transplanted into its abdomen, in which experiment it was noted that the central portions of the transplanted tissue underwent the usual degeneration, but the peripheral parts remained to some extent, grew, and were absolutely essential, by reason of their function, to the life of the animal. From many observations we know that transplantation of the thyroid can be complete and perfect. Experiments with the **mammary gland** have been equally successful, the transplanted glands becoming enlarged and secreting milk with pregnancy.

The transplantation of the **ovary** has met with almost as great success, although the central portions again are subject to necrosis; we are not in a position, however, to state how long the ovaries so transplanted continue to functionate. Experiment has actually succeeded in having ovulation follow an isoplastic implantation of ovary in a hen whose ovaries had been removed, and one case is on record of a similar happening in the human female, although the case has been given another explanation. From these and other experiments it seems proved that the continued growth of the grafted ovary will occur only if functional activity be demanded of it; should an isoplastic implantation of the ovary be made where there is still original ovarian tissue functionating, the transplanted tissue will be absorbed; if, however, the transplanted

tissue be called upon to functionate it will live. It will, of course, occur to the reader that autoplastic transplantation is likely to be more successful than isoplastic, because we know that in many cases the tissue juices in one animal are cytolytic to the tissue of another, and this antagonism will hasten the absorption of the graft.

The Skin and Skin Grafting.—The facts with regard to skin transplantation are well known; the capillary layer or part of it must be transplanted to obtain the best results. Although a certain proportion of mere surface parings will become the centre of new growth, the greater part of the graft, of course, dies, but very soon after transplantation the cells of the Malpighian layer are seen to show mitosis and multiply, spreading out from a centre of activity, the cells so spreading having actually amœboid properties. The new skin so formed, however, does not contain any of its more differentiated constituents, that is, hair follicles and sweat glands are not reproduced. We suppose that this skin is somewhat permanent, but we are met by such an experimental observation as this: if unpigmented skin be grafted into a pigmented area it may take, and will be at first unpigmented, but subsequently will become pigmented. This may mean that there is a subsequent replacement of the graft, piecemeal, by cells derived from the original epithelium of the host, that is, that the permanence of the graft is only apparent and not real. In support of this it may be said that in no case is the skin of another species successfully grafted on man; nevertheless, the mere presence of an animal graft seems to stimulate the skin cells of man, causing them to spread more rapidly than usual over the denuded surface. This may be another instance of that phenomenon to which we have previously referred, namely, that cells of like order attract one another; that is, that the presence of epithelial cells in the centre of a denuded area by **homotropism** attract the epithelial cells of the host around the edge of the denuded area. It may be that the diffused products of activity of the grafted cells act like allantoin (Macalister) as *cell proliferants* or *auxetics,* Ross having shown that the dissociation products of proteins stimulate cell proliferation.

Transplantation of Mucous and Serous Membranes.—The mucous membranes are quite as apt as the skin in transplantation, and the mucous membranes of the lips and of the mouth have been used to supply denuded areas on the eyelid. Similarly autoplastic grafts of the great omentum have been employed successfully to cover peritoneal wounds as also, recently, of fascia and tendons.

Transplantation of Teeth and Bone.—Transplantation of teeth and of bone properly speaking does not occur, being really implantation. It is of interest that the Romans understood the implantation of artificial teeth, and for many centuries in India teeth have been taken from one person and implanted in the jaw of another. The results are equally good, whether the tooth be newly drawn or one in which the pulp has been removed, or one that has been out of the body for

many years; in other words, it is not an organic union, but rather that vessels, nerves, osteoblasts, etc., penetrate into the pulp cavity, the tooth proper continuing to be an inert substance, which in some cases becomes absorbed, with failure of the procedure. Much the same state of affairs is found in the implantation of bone, sterilized bone or decalcified bone; such bone, like any other porous material, is merely a framework which fulfils the functions that the fibrin fulfils in the blood clot with the additional quality of rigidity and consequent preservation of the contour of the part.

Transplantation of Periosteum and Perichondrium.—Osteoplastic transplantation of these is very successful, especially if the periosteum be retransplanted upon an old bone, or into an area where bone has existed. Even isoplastic transplantation may be successful, but it is notable that in any experiment a good many of the periosteal cells may die, the burden of proliferation remaining upon those that survive. The bone marrow lends itself perfectly well to autoplastic transplantation, giving rise in its new site (*e. g.,* experimentally, the anterior chamber of the eye or the abdomen) to true bone.

Transplantation of Fascia.—One of the most serviceable recent advances in transplantation is the employment of fascia, particularly of fascia lata from the thigh, to replace tendon (*e. g.,* the tendo Achillis), and to reinforce weak areas, as for example the dura mater after removal of cranial bone by trephining.

Transplantation of Vessels.—In the last few years with improved surgical technique, numerous observers have successfully intercalated short lengths of arteries or veins in the course of other vessels. They have even obtained apparently successful results where the introduced segments have been killed by the action of formalin and other agents. Where the living tissue has been employed and the operation has been autoplastic there has been persistent vitality and even growth of the introduced tissue—indeed, portions of the autoplastic vein introduced into the course of the artery show pronounced connective-tissue hypertrophy, especially of the adventitia. Dead tissues, on the other hand, become surrounded by the new connective tissue of the host and undergo gradual absorption. This condition is one, not of transplantation, but of implantation.

Carrel's Experiments.—No consideration of transplantation at the present time would be complete if mention were not made of the surgical wizardry of Carrel in the transplantation of organs and even of limbs. Not only has he transplanted fresh organs with success, but even organs that have been preserved for many hours on ice, the vascular anastomoses being made with so wonderful a degree of skill that success has been attained; however, it must be admitted that save under the most favorable conditions of auto- or isoplastic grafting, there is an almost insurmountable tendency to subsequent atrophy and degeneration. Apart from the triumph of his surgical technique the greatest value of Carrel's work is his demonstration of the value of a good vascular supply toward successful transplantation.

Growth in Vitro.—In this connection it is necessary to call attention to the fact that tissues removed from the organism are capable of growing not only in or upon the living bodies of other individuals, but actually in lymph and blood serum removed from the body. The first observations were those of Ross Harrison, of Johns Hopkins, now of Yale, upon the embryonic nerve cells of the frog. Placing small pieces of neural groove of the developing tadpole in frog lymph he saw and followed the growth outward of the axis-cylinder processes. This work has been extended by Burrows, Carrel, Lambert, Klotz and others, and valuable studies have been made upon the growth of connective-tissue cells, epithelia, leukocytes, and even tumor cells. By transplanting to fresh media at proper intervals, cells may be kept growing and multiplying for weeks and months: each tissue is seen to have its characteristic mode of growth: mitoses occur. Cells can be seen to gradually gain the power of ingesting foreign cells (*e. g.*, the erythrocytes of another species) and following upon this to form and discharge lysins, the medium of growth gaining, for example, hemolytic properties after a few days.

METAPLASIA AND HETEROPLASIA

Metaplasia.—Metaplasia is the post-natal production of specialized tissues from cells which normally produce tissues of other orders, and is an adaptation on the part of cells to an altered environment. It is a constant physiological process, as is shown by the transformation directly of cartilage cells and cartilaginous tissue into bony cells and bony tissue. Yet metaplasia is bounded by certain rigid laws; *epithelial tissue can be converted only into other forms of epithelial tissue, mesoblastic tissue only into other forms of mesoblastic.* Epithelium and gland cells, for example, can never become converted into bone or cartilage, or *vice versa;* and even in the transformation of one form of epithelium into another we do not find that very wide gaps are bridged, as, for example, that simple epithelium should give rise to complex glands, nerve cells, or to the formation of hair roots. Fibrous connective tissue has never been seen to change into muscle, striated or non-striated.

A striking example of metaplasia is that if an eye be rendered functionless by trauma there will often develop from the choroid coat a deposit of true bone. Of course, bone in this region is normally absent, and its presence has been accounted for variously. We mention three theories, the first of which we consider the most acceptable. These theories are: (1) that the bone formation is due to modified function and nutrition of certain choroidal cells; these cells have normally a definite function connected with the receiving of light by the eye; this function being interrupted, the vascularity of the choroid is modified and certain of the choroidal cells give themselves over to the production of bone; (2) that in the process of formation of the eye a few cells destined to

form bone, being accidentally carried into the eye, remain latent so long as the eye performs its proper functions, becoming active when these functions are interfered with; (3) bone-forming cells are carried to the part by the blood. The remarkable frequency with which this bone formation occurs in the choroid of eyes which have been rendered useless by injury is strangely opposed to the two latter hypotheses.

Before discussing metaplasia specifically, it is necessary to separate one or two conditions which are not true metaplasia, but which might be confounded with it. The first of these is **heterotopia**, which may be congenital or acquired and consists of the abnormal snaring of cells of an organ from the organ proper, and their subsequent growth in another place. Examples of the congenital form are the various *cell rests* of Cohnheim, aberrant adrenals and accessory spleens; examples of the acquired forms are periosteal and bony growths from displaced perios- teum. It is to be noted that in none of these cases is there tissue transformation, for the tissue continues to grow along the ordinary lines; further, one sees the same process in the invasion of one tissue into the territory of another, in such a case as where, after tracheotomy, the epidermis may not only cover the wound but grow some little distance into the trachea.

Heteroplasia.—This is the condition in which we find in the middle of the œsophagus normally lined by squamous epithelium, islands of columnar epithelium like that of the stomach. No conversion has occurred from one type of epithelium into the other, but there is merely a persistence of characters and cell relationships peculiar to an earlier period of growth. The same explanation holds for the occasional islands of squamous epithelium found in the respiratory passages, and the stomach, without any evidence of past inflammation which might account for the change.

Reversionary Atrophy ("Undifferentiation").—To be distinguished from metaplasia is the loss of differential characters by cells which have become subject to abnormal conditions, for example, the sim- plification of the tubular cells of the kidney in nephritis, or the cubi- cal form of the lining cells of the pulmonary alveoli in interstitial pneumonia. The same process is illustrated by the development of mucoid tissue in the adult body, for mucoid tissue developmentally is an intermediate stage in the growth of another mesoblastic tissue. A similar process is the morphological change of cells due to mechanical action, *e. g.*, the flattening of a cubical or cylindrical epithelium in a cyst on account of the pressure of its contents. Again we must not confound with true metaplasia the differentiation of a tissue under modified environment without any change in the function, as occurs, for example, in the cornification of the epithelium of the prolapsed vagina. Metaplasia, in opposition to this, comprises both a morpho- logical and a functional change. Where, as in tumor cells, this simpli- fication has associated with it an incapacity to regain full differentiation and subsequent cell generations at most retain the imperfect develop- ment of the parent cells, we speak of **anaplasia**.

Epithelial Metaplasia.—The mucous membrane of the uterus is a columnar epithelium; if the organ be everted so that it projects from the vagina, its mucosa becomes smooth and dry, and in place of the columnar there is a stratified squamous epithelium with horny change of the external layers. Here, it will be observed, there is a change of function as well as of structure. In the bladder we find changes of two sorts; normally it is lined by polygonal epithelium in several layers. We may find over an enlarged prostate, as a result of inflammation, areas of typical squamous epiderm, with prickle cells, or, on the other hand, we may find papillomas developed with epithelium that is now distinctly columnar.

FIG. 130
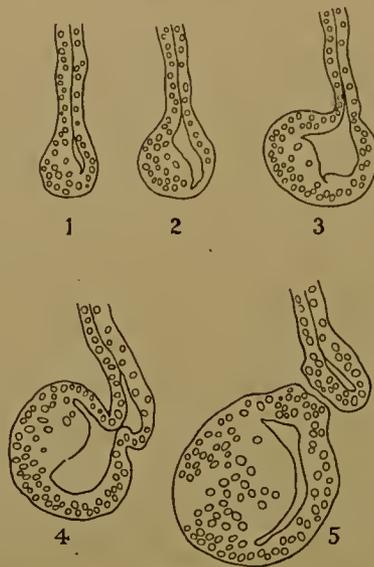
Stages in the metaplastic regeneration or formation of a new lens from the iris, in the larval newt: 1, edge of iris becoming swollen; 2, 3, 4, progressive overgrowth of the edge; 5, separation of the hypertrophied mass of cells to form the lens. (Fischel.)

In cases of ectopia vesicæ simple glandular crypts may form from what was a many layered epithelium. Even more remarkable is the metaplasia observed in the regeneration of the lens. In the larval newt, if the lens be extirpated, a new lens may be developed from the iris, as will be readily understood from Fig. 130. This is not very remarkable when we remember that the normal lens and the iris though differently formed are both epiblastic.

Mesoblastic Metaplasia.—Here may be seen the metaplastic formation of bone from cartilage, as occurs in the tracheal cartilages in advancing age, the one tissue being merely converted into the other. A similar process is the replacement of cartilage by bone in the callus of a fracture. A more striking example is the formation of bone by metaplasia of connective tissue (Fig. 132), as occurs in the formation of masses of true bone in the lung, or of plates of true bone in old pleural and pericardial adhesions, where there has been an excessive formation of granulation tissue. Both bone and cartilage further have been met with in the arterial wall and in the thickened valves of chronic endocarditis.

Should further example be necessary it exists in the replacement by bone of the tendons of origin or insertion of the muscle, as in the so-
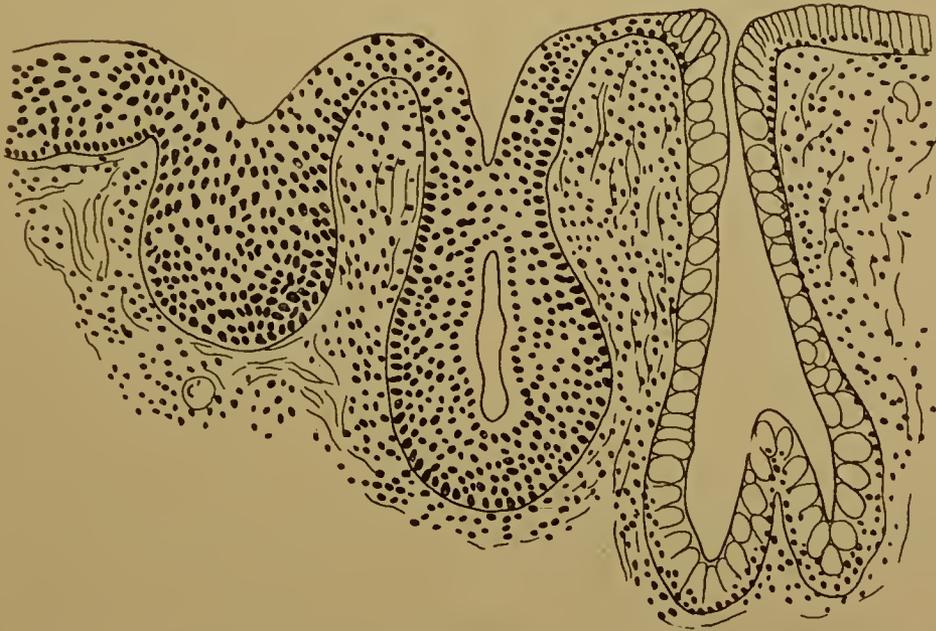
Metaplasia from a case of ectopia of the bladder; the ordinary stratified epithelium becomes replaced by a columnar epithelium. (After Enderlen.)

Osseous metaplasia in the wall of a bronchus (so-called "osteoma"): *a*, mucosa; *b*, submucosa; *c*, mucous glands; *d*, cartilage; *e*, connective tissue; *f*, *f*, masses of bone in submucosa; *g*, fat cells. (Dennig.)

called "rider's bone" of cavalrymen. This is purely local, but the same process is probably at work in the production of that remark-

able condition mistakenly called **myositis ossificans**, in which the tendons and bodies of one set of muscles after another become replaced by bone until finally the patient is unable to move his limbs, rotate his head, or bend his back.

As has been referred to above, the development of the provisional callus of long bones after fracture is an example of cartilaginous metaplasia, and the same is seen in the occasional islands of cartilage found in new growth derived from the connective tissue, especially in the mixed tumors of the parotid and the testis. We are fully aware that this is generally ascribed to the presence of cell rests, but there seems no reason to separate it from other cases of metaplasia.

Hitherto the examples given have dealt with the metaplasia of less specialized into more specialized tissues, but the reverse occurs, as when in an inflammation of the joint with immobilization, the cartilages disappear from the joint surfaces and are replaced by fibrous connective tissue. This is not a purely degenerative change, because inactivity of the joint would tend to atrophy, but results from a change of function, the immobility of the joint doing away with the necessity for cartilage.

In true metaplasia, finally, we have no new process, because bone arises first in the foetus from mesoblastic cells; even in the periosteum of the adult the future bone corpuscles may be indistinguishable from fibroblasts and in delayed union they may actually be converted into connective-tissue cells. In foetal life it is their environment and relationship to the vessels which lead certain mesenchyme cells to become osteoblasts and marrow cells. Why may not the same reason be in existence later? A difficulty does present itself in the idea of fully formed cells of one order becoming directly converted into cells of a different type, *but this does not happen;* metaplasia is not direct, but can be brought about only by a *preliminary reversion to a vegetative type of cell,* or, where mother cells are present, by the development of cells modified by environment. When we speak of the direct conversion of cartilage into bone cells we mean that in these histologically simple cells there is at least a functional change; that this is not merely a supposition is shown by the change in the matrix which they govern, and by its exhibiting a regressive modification.

THE NEOPLASMS

The term "tumor" is properly applied to any unusual swelling in the body, and includes (1) dislocated parts; (2) collections of fluid or gas; (3) tissue growths, either physiological, as the pregnant uterus, or hypertrophic, and others such; obviously, then, it can have no useful specific meaning applicable to the class of growth we wish to describe, a class which Thoma called the "autonomous tumors," that is, tumors which are, or possess a law unto themselves. These are now generally named the **neoplasms**, or new growths, and the process by which they

arise is known as **neoplasia**. But even these terms are not satisfactory, since there may be new growth set up by known agents. The tubercle, for example, is an inflammatory neoplasm due to the action of the B. tuberculosis. Despite these limitations it is usual to employ the term "neoplasm" to indicate the autonomous tumors and "inflammatory neoplasm" to indicate tumors due to the action of known agents, and in the following pages we shall fall in with custom. The neoplasms proper, therefore, are to be distinguished from inflammatory neoplasms by this autonomy, by their growth independent of function and of their nourishment, and by the fact of their arising either independently of any known stimulus or of their continuing to grow and develop after that stimulus has ceased to act: remove the cause and an inflammatory neoplasm undergoes regression and absorption—this appears not to be the case with true autonomous tumors. In the matter of terminology we employ the suffix—**oma** which cannot be exactly translated, but which conventionally carries with it the idea of a swelling, and more specifically, of a swelling of the above-described neoplastic nature, although exceptions occur in the case of such words as **hematoma**.[1] With more propriety than in the last named, the termination bears some of its full meaning in terms like **granuloma** and **tuberculoma**, for these are "tumors of granulation tissue" and "of tuberculous tissue" respectively.

To gain an idea of what neoplasms are, it is by no means a bad method to read over some of the various definitions that exist. Cohnheim described neoplasms as "circumscribed atypical productions of tissue from . . . embryonic elements," stating thus that they arise essentially from "cell rests," an idea largely given up at the present day. Ziegler states that "a tumor is a new formation of tissue, possessing an atypical structure, not exercising any useful function, and presenting no typical limit of growth"; Lubarsch counted them to be "growths of apparently independent origin, histologically corresponding with the cells of the matrix from which they arise, but atypical in form . . . "; von Rindfleisch characterized them as "local degenerative excess of growth." Perhaps these ideas are best grouped in White's definition, that a neoplasm is "*an (abnormal) mass of cells, tissues, or organs, . . . resembling those normally present but arranged atypically. It grows at the expense of the organism without subserving any useful function.*"

Accepting this definition, how are we to proceed to treat this important subject? In dealing with the infections we proceeded according to causative agent. That was the natural course. Here it is a matter of familiar knowledge that we are largely in the dark regarding the causation of "tumors;" the little that we know at the present time only serves to make confusion worse confounded. We are bound therefore to fall back upon an anatomical or histological classification. The majority of recent writers, indeed, content themselves with a purely histological classification, but since a large proportion of new growths and that

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[1] A local accumulation of blood in the tissues.

clinically the most important, possess characters not of fully formed tissue elements, but resembling one or other stage in the development of one or other tissue, we are convinced that a histogenetic classification and treatment is both more scientific and more serviceable. We are convinced further that this treatment aids us in comprehending the nature of new growths. That from imperfections in our knowledge it has defects, we freely admit, but at the same time recognize that it is both less defective and represents a higher scientific ideal than the mere haphazard enumeration and treatment of the diverse histological types of cell growth. So again it might seem simpler to begin with the description of what histologically are the simplest types of neoplasm. Our experience makes us believe that a fuller grasp of the subject is by beginning with what embryogenetically are the simplest, and histologically are the most confused and confusing.

We shall therefore discuss these autonomous new growths in the following order:

1. The *Teratomas*, tumors derived from *totipotent* cells, from cells, that is, capable of giving origin to tissues of all orders, and containing cells and cell complexes derived from all three primitive germinal layers.

2. The *Terato-blastomas* or *Mixed tumors* of Wilms, tumors originating from *multipotent* cells, from cells capable of giving origin to tissues of more than one order, but incapable of giving rise to representatives of more than two at most of the three primitive layers.

3. The *Blastomas* or ordinary tumors, originating from *unipotent* cells, capable of giving origin to one order of tissue only. With these we shall consider a condition usually included among the tumors proper, which nevertheless is a border line condition, that, namely, of *hyperblastosis*.

THE TERATOMAS

These are neoplasms which show a tendency to the formation not only of irregular cell masses but also of fully formed organs such as brain, teeth, skin, hair, bone, or secreting glands; for example, a cyst-like mass containing many of these tissues may be found in the ovary— the ovarian dermoid. All monstrosities are terata, and such will be found discussed in the appendix down to the case in which, of two individuals from a common ovum, the feebler of the two becomes infolded into the stronger, and takes its nutriment from it. Such a foetal inclosure is a typical teratoma. It is not an independent individual; it is incomplete; it is nourished from its host; but *it began its existence as a separate individual*, from a separate primitive streak. It may quite well be that both host and parasite arose from a single act of fertilization, but at an early period of development two independent centres of growth showed themselves, and it is the autonomous growth of one of these within the other that has given rise to the mass of tissue constituting

the parasite. The teratoma is thus "*an autonomous growth, the product of the continued development within one individual of another individual of the same species*," the term "continued development" being inserted to exclude the normal fœtus.

Before considering teratomas specifically, it is worth while to note what kinds of cell in the body in its different stages are capable of giving rise to all the orders of cells that go to make up the individual. At first glance one would say that the fertilized ovum alone can do this, but totipotentiality is more extensive than this. A **totipotent** cell is one that is capable of giving origin to an individual, that is, one that can give origin to cells of every order; a unipotent cell is one that can give rise to cells of only one order. The following are totipotent cells: (1) the primordial blastomeres, which, even among vertebrates, if broken off, can give origin to individuals, though dwarfed; (2) the cells of the primitive germinal area; (3) the cells of the growing point, so long as they remain in connection with the ovum (this by reason of their containing no yolk); (4) the germinal blastomeres, that is, the forerunners of the ova and spermatozoa, and (5) the mature ova and spermatozoa after fertilization. We have to consider, then, that there are, subsequent to the fertilized ovum, these various sources from which a teratoma can arise; the forms that can arise, some of which have already been dealt with, are as follows: (1) development of two germinal areas on one germinal vesicle, giving rise to double monsters, one of which undergoes inclusion in the other—**fœtal inclusion**. (2) The production of excess or misplaced totipotential cells which become included in the growing individual; these cells may develop early and grow elaborately, giving rise to *inclusions recognizable at birth*, or may lie latent and at a subsequent time grow actively, as *abdominal inclusions, teratomas of the genital glands*, and certain "*mixed tumors*." These various teratomas require more particular note.

Fœtal Inclusions.—These inclusions may be complete or incomplete and projecting; the weaker and smaller embryo is carried into the body of the larger during the process of closing of the great anterior fissure.

Epignathus and Congenital Sacral Teratomas.—Some wonderfully complicated cases are found under this class, such as where there is inserted into the *roof* of the mouth of one fœtus the umbilical cord of the second, more or less well developed, or where definitely formed organs, lower limbs, or sexual organs project from the mouth; less curious are those where projects a mere mass of flesh in which can be distinguished tissues of the various kinds that are ordinarily derived from all three layers of the embryo—the most common form of **epignathus**. Sometimes there is merely a tumor of the roof of the mouth, in which the tissues are simpler, and do not represent all three of the primitive layers. This last may have arisen not from totipotential cells separated at an early stage, but from multipotential cells separated at a later period.

Teratomas of the Genital Glands and Sporadic Teratomas.—This class comprises some cases that are clinically very curious. The

cases mentioned above of cysts containing hair, teeth, etc., being found in the ovary, are surpassed by the discovery of similar tissues in the testis of the male. Of such neoplasms we find that some grow in parts of the body bearing no relationship to the fissures or to the poles of the body, or to the generative glands, as, for example, in the neck, the anterior mediastinum, the abdomen, and elsewhere. No rule can be laid down for these, and we are able to say only that there must have been a development of displaced totipotential cells. These teratomas—called *sporadic embryomas*—consist generally of tissues from all three germinal layers; sometimes the tissues are of adult appearance and of limited growth, and these are called **typical**; more frequently, however, they are **atypical**, appear about puberty, grow rapidly, and tend to form secondaries. This, it will be noted, is exactly parallel to the occurrence of benign and malignant blastomas to be hereafter mentioned. Sometimes a tissue in a typical teratoma of this sort will begin to grow inordinately, the result being a neoplastic growth in a neoplasm (**tumor in tumore**). A tumor of this order may give rise to distant metastases in the body of the host.

Most commonly teratomas are found in the ovary, and are of two forms: (1) the large-cystic teratoma, commonly called the "**ovarian dermoid**," and (2) the solid or small-cystic teratoma. The former is the commoner and may come to be a foot or more in diameter; its contents are fatty debris and long hairs lying in a varying amount of fluid. It is lined by squamous epithelium with sebaceous and sweat glands, with bone frequently to be found in the walls and an area which has been called the "island," representing the head; from the island arises the tuft of hairs (in our experience, always red), and in it may be bone in which are fastened teeth. In a small number of cases the extremities and genitalia have been recognized. Typical ovarian teratomas of this kind may be found in young children. The solid ovarian teratoma is like the sporadic teratomas already spoken of, and is very uncommon.

With regard to teratomas of the testis, it remains to be said only that the so-called mixed tumors of the testis have frequently been found to belong to this class, and close study is apt to reveal tissues from all germinal areas. These are evidently the product of totipotential cells.

It is difficult to account for such peculiar freaks as these when they appear elsewhere than in the ovary and testis without calling to our assistance, as an explanation, the disappearance and displacement of some of the germinal blastomeres, because we know that these in the process of development do not all find their way into the ovum or the testis; they may be carried and deposited in different parts of the body. We need not imagine any carrying away to account for the teratomas of the genital glands, because this is the natural site of these totipotential cells.

THE TERATOBLASTOMAS

These are neoplasms which are not true teratomas, because the tissues in them do not represent all three germinal layers; they include the most striking examples of the "mixed tumors,"[1] although not all of them. It must be kept in mind that there are several orders of "mixed tumors" to be distinguished: (1) the teratomas, (2) the teratoblastomas, (3) the transitional lepidomas (p. 391), and (4) the carcinoma sarcomatodes proper (p. 383). We owe to Wilms the fullest study and clearest explanation of the type here being discussed: they may be termed the mixed tumors of Wilms. A very familiar form will occur to

Fig. 133
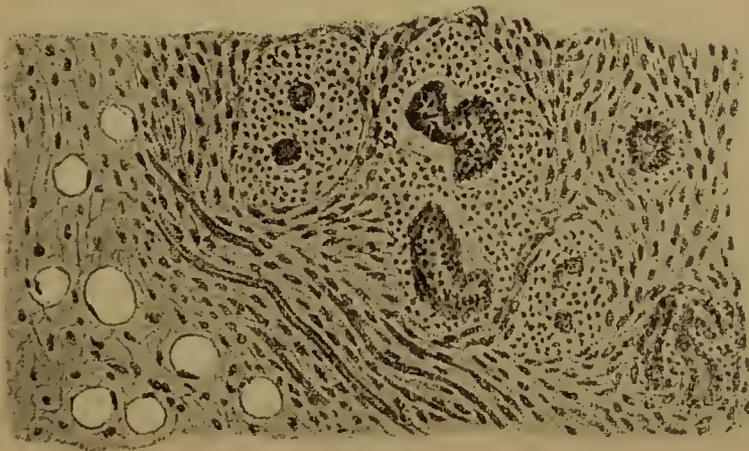
Section of a "mixed tumor" of the kidney, showing gland tubules with surrounding sarcoma-like cells of the plain muscle type, fat cells, etc. (Ribbert.)

the reader if one mentions the so-called "sarcomas of the kidney," which have been noted so frequently, growing to large size in the infant. In this and in mixed tumors of like order arising in different parts of the body one must make the broad statement that one finds in such a tumor only tissues such as might develop from the original *anlage* of the organ; by this we mean that just as the kidney arises from certain myotomes which give rise to various structures in the neighborhood of the kidney, it is impossible to find in a renal tumor a tissue that is not potentially represented in the myotome. Such a tumor has originated from the misplaced myotome cell which, developing later, gives origin to all the orders of tissue which would have developed from it had it undergone growth in its normal position.

It is obvious in such a tumor as this, that is, one arising from the myotome, that all the contained tissues are necessarily mesoblastic. These neoplasms are large, localized, soft, sarcoma-like, and bleed and necrose readily; on section, the body of the tumor is sarcoma-like, but there are in it elements that recall a kidney tubule, as well as muscle, fibrous and elastic tissue, fat, cartilage, and so on. Mixed tumors of a like nature in which the tissues vary according to the situation,

are found in the parotid gland fairly commonly, less so in the sub-maxillary gland, in the vagina in children, in the cervix uteri later in life, in the mammary glands, the lacrimal glands, the cheeks, and the gums.

THE BLASTOMAS

(1) Teratogenous Blastomas

By this term we indicate tumors formed of one order of cell, but originating not from the tissues of the host but from that of another individual or potential individual within the host. The simplest example is that of an adenoma or carcinoma developing from an ovarian teratoma; the most interesting and important are those developing from the placenta, viz., placental moles and chorio-epithelioma. To use simple language at the cost of being slightly inaccurate one may explain that the latter is an interesting form of tumor arising where the rapid cellular growth of the placenta is not checked at the birth of the fœtus, but continues growing in the uterus, producing a most malignant and fatal neoplasm. One might say that fœtal structures habituated to rapid growth continue in the uterus after their physiological purpose is fulfilled, and become to all intents and purposes a neoplasm of the blastoma type.

The fœtal membranes include the fœtal placenta, which is an organ developed primarily from the chorionic villi; being epiblastic, it comes, with the development of the allantois, to gain a vascular mesoblastic core. Before the placenta develops, the outer cell layers of the fœtal chorion have "eroded" into the uterine mucosa. The actively growing cells of the outer layer of the villi are phagocytic and penetrate into the sinuses of the uterus below the mucous membrane. Normally, these cells, when they have penetrated into the sinuses, have done their work and the outer layer becomes inactive, fuses and forms the syncy-tium; below this at the time of birth there are still layers of active cells—the so-called Langhans' layer—but these also undergo degeneration and in the due expulsion of the placenta at parturition they come cleanly away from the uterus. But in cases of abortion it some-times happens that these placental changes, usually complete by the time of full term, have not yet occurred and when the immature fœtus is expelled, there remain chorionic cells which have not degenerated and are still actively growing. These constitute the evil agent, and they carry on their growth in the uterus and constitute a neoplasm.

Placental Mole.—It sometimes happens soon after conception that the fœtus dies and is absorbed, leaving the placenta and membranes grafted upon the uterus, and these form an irregular fleshy mass, the **fleshy mole**, prone to hemorrhage (the **hemorrhagic mole**), and to subse-quent putrefaction (the **putrefactive mole**). Again, in similar cases the chorionic villi being nourished by the maternal blood grow actively and absorb fluid so that a villus becomes a vesicle or series of vesicles of small or large size distended by an œdematous mucoid fluid, these

vesicles being aggregated together in enormous numbers, the mass distending the uterus as much as does a full-term fœtus (**hydatidiform mole**). The vesicles are yellowish and translucent. Even in an otherwise normal placenta a small portion of it has sometimes been found to consist of such a mole.

Chorio-epithelioma. — In the case last mentioned it will be seen that the growth remained within normal limits, and was, therefore, of benign nature, but this is not always the case. Such a mole may continue to grow and fill the maternal uterine sinuses with polypoid masses, the so-called "**destructive placental polypi**," which show a kind of transition to the full-blown chorio-epithelioma malignum. We have said that the outer surface of the villus, consisting of fœtal epiderm, becomes fused to form syncytium, which is made of deeply staining cells whose bodies have fused, the mass remaining multinuclear. Below the syncytial layer the cells of Langhans' layer remain unfused, individual, and less deeply staining. The syncytium

Fig. 134
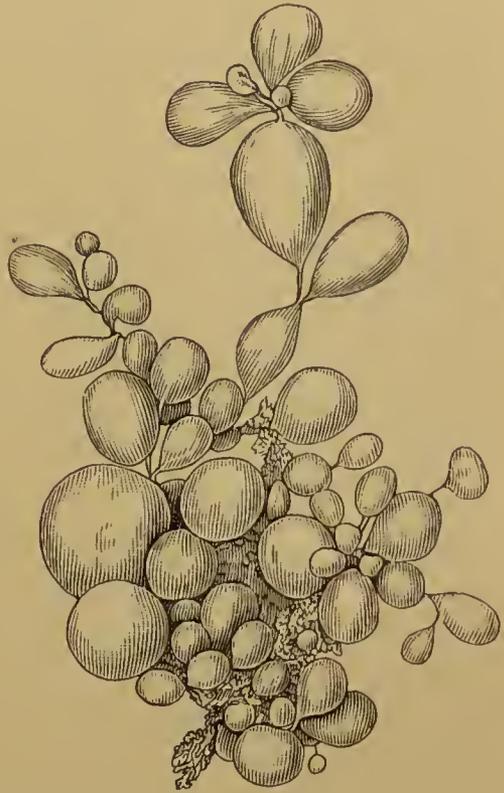
A small portion of a hydatidiform mole; natural size.

Fig. 135

Chorio-epithelioma growing within the uterus: *V*, wall of uterine sinus; *Syn.*, multinucleate cells of syncytial type; *L. c.*, cells of Langhans' type. (Teacher.)

possesses erosive phagocytic properties, and it is these masses of cells that tend to be swept away in the blood of the maternal sinuses and to

be deposited in the capillaries of the lungs and elsewhere. Thus we have these syncytial cells growing actively either in the uterine sinuses or in tissues elsewhere, the active growth of the syncytium being seconded by the activity of the cells of Langhans' layer. The **chorio-epithelioma malignum** is thus seen to be a neoplasm entirely cellular, formed of large actively vegetative cells growing entirely within the vessels, not requiring an individual blood supply by vessels of its own, not capsulated, liable to induce hemorrhage by erosion of the vessel walls and very readily tending to have particles carried away to grow elsewhere. With such characteristics it is no wonder that we have here perhaps the most terribly fatal of all neoplasms. Although the formation of this neoplasm generally occurs shortly after an interrupted pregnancy, yet cases have been reported occurring years after abortion, no intervening pregnancy having occurred.

FIG. 136

Cells of a chorio-epithelioma malignum, higher magnification: *a*, syncytial cell mass; *b*, cells of Langhans' type; *c*, broken-down erythrocytes. (Von Franque.)

The difficulty of understanding such a process of growth is increased by the finding of this growth in the testis of the male. Here the explanation must be that cell masses of this type have developed, not as the outcome of the fertilized ovum and uterine pregnancy, but from a teratoma. The teratoma must develop or tend to develop a chorion and so gain its nourishment through this chorion, invading the veins of the testis; the chorionic cells so developed may proliferate in the testis just as they would in the uterus.

In like manner, a few cases have been described within recent years in which sporadic teratomas in various regions of the body have been found on examination to afford chorio-epitheliomatous areas.

(2) Ordinary Autochthonous Blastomas

The commonest form of tumor is the indigenous or autochthonous blastoma, composed of cells of one order derived from the tissues of the individual host; yet these neoplasms contain a stroma (just as do the tissues which may be said to be all stroma; for it is such simple connective tissue that forms the stroma of organs). With this exception, the blastomas are growths formed of one order of tissue, and are in number as many as and more than the different tissues; for example, fibro-

blastomas,[1] or fibromas of fibrous tissue, chondromas of cartilaginous, and osteomas of bony tissue; myomas of muscle fibres, gliomas of glia cells, adenomas of (secreting) glands. *There are many more forms of blastoma than there are forms of individual tissue*, because the cells of a neoplasm, originating from a special kind of cell, may not present the characters of the original cell fully differentiated. They present different degrees of approach to the fully formed and fully differentiated cell of the original tissue. When the neoplasm approaches closely the form of the adult normal tissue, we speak of it as **typical**; when the neoplasm copies this but imperfectly, when the cells are but partially differentiated, when the neoplasm is like no adult normal tissue (but has for its counterpart cells seen only in the embryo) it is **atypical**. Further, as a general rule, the blastomas that are of the type of normal adult tissues, the typical tumors, are also the **benign** tumors; and the cells that copy very imperfectly the normal adult tissues, and sometimes copy faithfully enough the growing embryonic tissues, the atypical tissues, are also the **malignant** neoplasms.

Benign Neoplasms.—The typical blastoma is composed of cells and tissues that are like the cells and tissues of the normal adult body. They are neoplasms in that there was a time when they did not exist, and they have arisen for no apparent reason and in response to no known stimulus—they are **new growths**; but they are like normal tissues because they reproduce the differentiations of normal tissues, and, as such, have grown slowly, and this slowness allows the body to react by producing a wall around them, a capsule, which is essentially a part of the body tissues, and not of the neoplasm. Some tissues, such as brain or bone, are incapable of free fibrous overgrowths, and do not readily produce a capsule, but, as a general rule, most tissues are able to circumscribe the growth, so that such neoplasms can often be shelled out. The tissues being "typical," and like those from which they sprang, there is nothing essentially harmful in such a growth, save that it may by pressure or otherwise, mechanically disturb the tissues in which it lies. Growth, in such a neoplasm occurs in all its parts, central as well as peripheral, and thus there is a tendency to increase in a globular shape, with gradual enlargement in the same form.

Malignant Neoplasms.—Atypical blastomas, on the contrary, are formed of imperfectly differentiated cells, and because they are less differentiated, are more actively vegetative. They spend little energy on function or in the direction of differentiation and, consequently, have the more to expend on mere growth; active proliferation is, therefore, one of their main characters. Such rapidity of growth gives time for little reaction on the part of the surrounding tissue, and there is little

[1] Mallory urges the use of the term *fibroblastoma, chondroblastoma*, etc., in place of the time-honored *fibroma, chondroma*, etc., on the ground, we take it, that it is the type of cell rather than the type of tissue that is the prominent feature in these blastomas. With this reason we are wholly in agreement, but doubt whether this is not already recognized sufficiently well to render the additional syllable unnecessary.

sign of encapsulation; even if a capsule appear to the naked eye, it is apt to be **infiltrated** by the actively growing neoplasm; the rapid growth, meantime, by pressure causes atrophy of the cells of the organ concerned, and as these die, the connective tissue may remain as a scaffolding on which the neoplasm builds itself. The active growth, too, tends to invade capillaries or lymph channels, so that cells or groups of cells may break off from the neoplasm, and be carried elsewhere in the body, where, finding suitable resting places, they go on with their growth and form new masses or tumors like the parent growth. Such new growths are denominated **metastases** or **secondary neoplasms.**

The impression gained from the above that the atypical tumors are malignant is almost correct; but it is only fair to add that the above characters, which are those of malignancy, do not belong to all atypical tumors, for there are malignant tumors such as rodent ulcers (facial epithelioma), and the malignant mouse cancers that do not readily form metastases and, on the other hand, there are tumors of benign type that form secondaries; we have, in fact, all grades of transition between typical and atypical neoplasms. Yet it is useful to gain the general idea that tumor-cell differentiation (or specialization of form) has a definite relation to benignancy, and the lack of it, that is, a tendency to the vegetative type of tissue, has a relation to malignancy. It is upon such evidence that the decision is made which determines the removal or otherwise of the tumor concerned. This being so, it is very essential to have a clear knowledge of what is the adult type of cell from which a particular tumor springs; for example, the so-called giant-celled sarcoma arising from the bone marrow, exhibits cells of a vegetative, indifferentiated type, and might on that account be called very malignant, until one recalls that the adult bone-marrow cells are of this type; this sarcoma, as a matter of fact, is one of the least malignant of all sarcomas; whereas, a melanoma appears to be made up of more differentiated spindle cells, and on this account might be judged of mild malignancy, yet is one of the most malignant of tumors. Emphasis must, therefore, be laid on the necessity for knowledge of the adult tissue from which a neoplasm is supposed to arise.

Malignancy.—It must be understood at the outset that it is not possible to lay down working rules by which a student may surely know whether a tumor is malignant or benign; such knowledge can come only from experience—from the "mental pigeon-holing" of a number of cases in each of which one correlates his ideas of the clinical history, the macroscopic appearance, and the microscopic picture, and his theoretic knowledge of location of tumors; these the observer mentally puts together as one ties up papers in an elastic band, and after he has correlated many such, he begins to reach a state in which his intuition tells him that a tumor is malignant or the contrary. Some of the rules that are of use are these:

Malignancy is associated with:

1. A vegetative character of the cells, that is, the cells are like the corresponding cells of the embryo.

2. Rapidity of growth.

3. Peripheral extension, with lack of capsule, and infiltration of the surrounding tissues.

4. Tendency to develop metastases.

All of these four qualities are related, and are the expression of a vegetative activity beyond that of the surrounding tissues.

5. Tendency to Central Degenerative Changes.—This can be readily understood, for the pressure of surrounding parts tends to constrict blood vessels, and the outermost cells obtain the best of the oxygen and food supply, while the inner ones are deprived of these, and also of a free outlet to their own end-products; the degenerative changes are atrophic, or necrotic, or at times autolytic, so that the central part of a tumor may become fluid. Similarly, in a surface tumor, the most superficial cells are farthest from the blood supply, and are therefore liable to necrosis.

6. Liability to Recurrence after Removal.—This arises from the fact that the removal is not complete; the infiltrating character of the growth leads to the extension along lymph channels of chains of cells in contiguity beyond the apparent boundary of the neoplasm. This is the reason for the modern radical and extensive operation undertaken, for example, in carcinoma of the breast.

7. Cachexia.—Cachexia is a lowered, impoverished state of the system, indicated by a marked degree of wasting and bodily weakening, with the characteristic yellowish-gray color of the skin, which is readily recognizable.

8. Anemia.—This goes hand in hand with cachexia, for which indeed anemia is partially responsible. There is a constant loss of red corpuscles, and sometimes the signs of regeneration show that the blood picture is not very different from that of a severe Addisonian anemia. Cachexia, however, is not necessarily in proportion to the size or the rate of growth of the tumor; a very small carcinoma may be accompanied by very severe cachexia, and certain, though small, neoplasms, if situated in the œsophagus, may interfere with nutrition in a physical way, so that the cachexia is thereby increased. This is not true cachexia, but rather starvation; nor is it correct to use the term "cachexia" to describe those cases where absorption of the foul products from the tumor surface have occurred; yet leaving these aside we still have the true cancerous cachexia.

Have tumor cells an internal secretion? The question is of importance because cachexia and anemia have been long considered as results of a specific toxic secretion of the tumor cells. Presumably these in their growth and in their degeneration discharge soluble substances into the body fluids. These are of the nature of enzymes, and as such are hemolytic and probably in some cases cytolytic as well,

so that we may assume that the cachexia is directly the outcome of poisonous products of cell activity.

In the above paragraphs we have given at least eight characters which have to do with malignancy, but we would once more add the caution that all of these may not be present, that the reverse of some of them may be found, and that some of these very characteristics may be seen in a benign growth, so that we have yet the essence of malignancy to discover. Is this something in the nature of the cell itself? We think so, although some scientists have declared on the contrary that there is no such thing as a malignant cell *per se;* but that cells have malignancy *per se* is proved by the fact that mouse cancer being passed through generations of mice can be rendered more and more malignant, so that there is a constantly increasing number of "takes," until finally 100 per cent. of animals injected develop the mouse cancer which has been conveyed to them. *The malignancy of cells is determined by the grade of vegetative power they show; the malignancy of any given tumor is the resultant of the interaction between cell malignancy and the resisting powers of the rest of the organism.*

There are yet other forms of malignancy (so-called) to consider. We have sometimes been tempted to define a malignant neoplasm as a new growth that tends to kill; if this be true, we are prepared to understand that there is *malignancy in virtue of site,* and *malignancy in virtue of size.* For example, a benign tumor that in the liver might be harmless, in the brain might cause death, or a large ovarian tumor benign in its nature may so press upon other organs as ultimately to kill the patient. This is obviously accidental malignancy. It must not be forgotten that a tumor typical and benign for a long period may suddenly assume in any one of its parts rapid growth, a statement which can be understood when we recall that malignancy is a function of the rate and extent of the cellular reproduction rather than of cellular proliferation itself.

Metastases.—We have become accustomed to consider as metastatic, inflammations in which the agent, bacteria for example, is carried to a distant part of the body where the tissues react to its presence, so that the metastatic inflammatory overgrowth is made up of the body cells; with neoplasms this is not the case, for the metastatic overgrowth is made by the multiplication of the cells of the original tumor in the new area. *The migrating cells are the parasites.*

It does not follow that the secondary growth need faithfully reproduce the parent growth. As a matter of fact it generally reproduces the type, but is often more actively growing, more vegetative and simpler in structure.

Modes of Origin.—Metastatic growths may originate in four ways:

1. The cells of the original growth penetrate into the lymph spaces and are carried in the *lymph stream* a greater or less distance and lodge in the lymphatic system, oftenest in the nodes. Sometimes in the neighborhood of the tumor small nodules may be found con-

nected with the original tumor by an unbroken chain of tumor cells; what has occurred is that the tumor cells have grown out continuously along a channel until they have arrived at some spot, often at quite a distance, where conditions of lessened pressure and good food material encourage them to grow as a localized mass (Fig. 137).

Fig. 137

Fig. 138
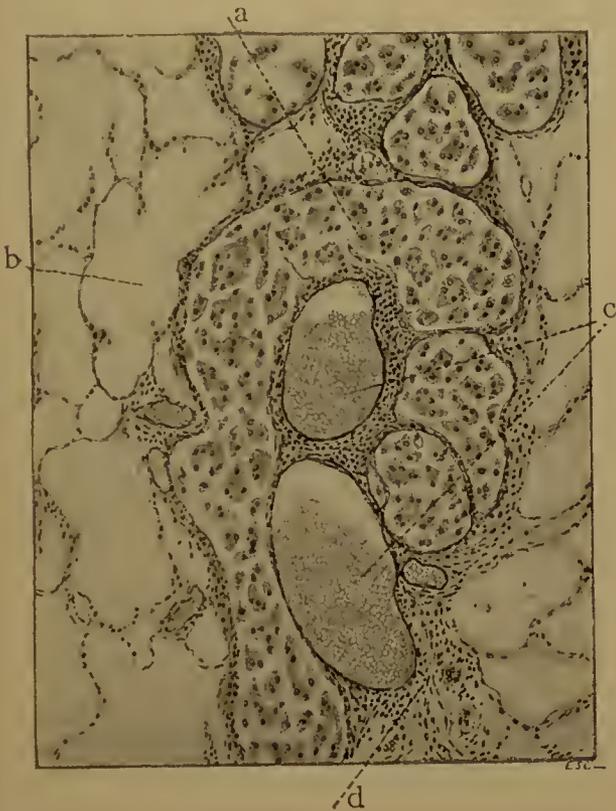
Carcinoma advancing along the perivascular lymph channels of the lung from a pleural growth secondary to carcinoma of the breast. (Dr. Rhea.) *a*, perivascular lymph vessel distended with cancer cells; *b*, alveolus of lung; *c*, blood vessels; *d*, secondary leukocytic infiltration of the perivascular connective tissue.
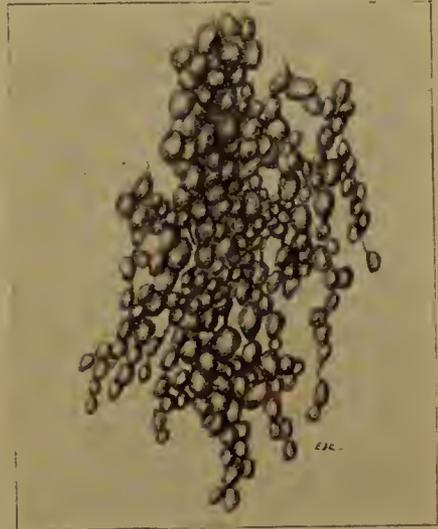
Group of nodular secondary growths of round-celled sarcoma peeled off from the surface of the peritoneum in a case where a general "seeding" of the perineal cavity had occurred.

2. The tumor in its growth may erode a vein and the cells may thus pass directly into the *blood stream* and be carried elsewhere. Such cells will be liable to arrest in the first capillary into which they are carried. Neoplasms whose cells are thus carried into the branches of the portal system are apt to form secondaries in the liver; those in the main venous system are apt to be carried to the lungs. Rarely cases arise which seem to indicate that here and there tumor cells may be carried through the lung capillaries without arrest.

3. By *transplantation*. This form of conveyance is but a modification of the first, because it occurs in the serous cavities, which are lymph spaces. If a tumor erodes the lining membrane of one of these sacs some of its cells may become free and be carried elsewhere in the same cavity, as is especially well seen in the peritoneum (Fig. 138). Transplantation has even been known to occur from tumors in the mouth

cavity being carried to the stomach, and tumors in the stomach being carried to the intestines. It is not safe to jump to the conclusion that a secondary in the small intestine has found its way there by transplantation even though the primary growth be in the stomach, for even here the extension may have taken place by the lymphatic channels.

4. Transplantation also occurs by *apposition*. Cases are recorded in which (a) one lip being involved in cancer, the corresponding point on the other lip has become infected; (b) the skin of the arm in contact with an ulcerating carcinoma of the breast has become involved; and in which (c) the parietes, *e. g.*, the pleural, opposite a superficial malignant growth have become the site of transplantation even when no adhesions between the two have existed. The process of rubbing has bared the second surface, on to which the cells from the first have become engrafted.

Retrograde Metastasis.—While the cells are generally carried by the force of the lymph or blood stream and the secondaries are thus situated farther down the stream, nevertheless, it may occur that such growth or carrying of neoplastic cells is in the direction precisely opposite to that which might be expected. Thus, in cancer of the breast one may find the head of the humerus of the same side infiltrated. Yet the head of the humerus sends lymphatics to the axillary nodes and not away from them, so that part of such extension must have happened against the stream. The explanation of this anomaly probably lies in the supposition that some direct channels are blocked and the neoplastic cells seek out collateral routes. We have to remember the possibility that the extension may occur by direct extension of growth along the lymph channels which we can imagine prevails against the lymph stream as well as with it; while where there exists a backward pressure in the inferior vena cava, the cells may actually fall back from the inferior vena cava into the hepatic veins.

Unicentric and Multicentric Primary Growths.—It is ordinarily not possible to follow a tumor to its earliest beginnings, but we have good reason for supposing that most blastomas arise from one cell or from a group of cells in juxtaposition, and neoplasms which thus grow from a single focus are **unicentric**. Others, however, appear to be **pluricentric**, that is, it seems that of a number of cells or of groups of cells near one another, each gives origin to an independent mass of new growth. This fact tells against the theory of cell rests, in that the adult cells of an organ are sometimes seen undergoing change into the neoplastic type.

We have also to admit that it is possible for one body to be the seat of **multiple neoplasms of different kinds** at the same time. It is hardly likely that these depend one upon another; more likely is it that a lowered bodily resistance permits cells of various kinds and in different parts of the body to undertake active proliferation. It is perhaps due to the same condition that we sometimes find bilateral organs affected by new growth of the same or similar kind. It is, of

course, possible that one of these is primary and the other secondary, the other organ being the organ selected because of what has been referred to as tissue predilection. There is a certain amount of evidence which suggests that in such a case both growths are primary.

Tissue of Predilection.—It is notable that in metastatic tumors some tissues are very likely to be affected, while others are almost sure to escape; an example is seen in the readiness with which melanotic growths appear in the liver, and the secondary tumors of the thyroid in the bones; the muscles are rarely involved in metastatic growths. The meaning of this is that not all cells carried to different parts of the body are able to proliferate, for often the ordinary cells of the body react against the newcomers, and it becomes a trial of strength between the two tissues, the proliferative power of the parasite being matched against the reactive power of the host. The vegetative powers of cells broken off from a benign tumor are not remarkable, and so in general the metastases from such a tumor do not eventuate; this antagonism, too, is not merely a local matter, but becomes a character of the body fluids, as is shown by the observation that in transplantation of tumors there are stages, during some of which retransplantation can be made, while during others such an attempt fails, owing, no doubt, to the existence of antagonistic, presumably cytolytic, substances in the body fluids.

The Production of Metastases by So-called Benign Tumors.—Certain tumors of benign type are able to cause metastases, e. g., the chondromas. Here we have multiple secondary tumors in the lung, clinically not dangerous. It is not possible that fully formed cartilage cells make their way into the pulmonary capillaries, but rather that the perichondrium cells (small actively growing cells that surround the periphery of a chondroma) which are small, are carried to the lung and there give rise to their normal product—cartilage. A like example occurred in the Royal Victoria Hospital, Montreal, where an arm had been removed for an osteomatous growth, and the axillary nodes were found converted into nodules of solid bone. Here it was the osteoblasts that had been carried by the lymph stream to the lymph nodes, where they had fulfilled their normal function. It will be at once evident how like this phenomenon is to true malignancy, although our clinical knowledge compels us to recognize it as essentially nonmalignant. Even a stronger example is seen in connection with the thyroid gland; in the bones have been found masses of thyroid tissue, actually producing colloid, replacing extensively the bone, having malignant properties, yet clearly benign in histological type, and strangest of all, careful search through the thyroid may have revealed no primary tumor. All of these cases cited above indicate a want of correspondence between structure and properties, and indicate that there are cases on the border line between malignant and benign tumors, which conform fully to neither group. A classification of tumors based upon the existence or non-existence of malignant properties cannot

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satisfy; however important it be from a clinical standpoint, it is necessary to find some other basis for classification.

Latency in Metastases.—It is seen from time to time that a neoplasm, successfully removed, may break out in metastases years after the operation. We have lately seen a case in which recurrence appeared eight years after removal of a melanotic sarcoma of the choroid. Have cells from the original neoplasm lain latent all this time? Presumably so, for the same phenomenon has been observed in transplantation experiments; the transplanted cells of neoplasms evidently either (1) grow immediately in their new surroundings, or (2) lie latent for a long time, with or without eventual multiplication, or (3) degenerate and are absorbed. The variance of these happenings indicates that metastasis depends not only on the inherent growing qualities of the neoplastic cells, but also upon the resistance of the tissues; the latter may be merely another way of saying, as was said above, that there is a predilection in tissues.

The Nature of the Stroma.—The blastomas gain their nutrition from the host and possess a blood and lymph supply. In what degree the intervening tissue belongs to the host and in what degree to the neoplasm is a matter for consideration. The capsule of the typical blastoma is formed by the tissues of the host; even in a typical blastoma the cells at first make their way between the supportive cells of the host, and the connective tissue of the host thus becomes the stroma of the neoplasm, and its cells grow side by side with the neoplastic cells. Just as in inflammation, a neoplasm infiltrating an organ may kill off the specific cells of the organ and at the same time stimulate the more lowly connective-tissue cells to proliferation, and this at times to so great an extent, as in scirrhous carcinomas, that the connective-tissue overgrowth acts as a direct check on the neoplastic growth. In an atypical connective-tissue growth (**sarcoma**) a double process is at work; the stroma itself multiplies, and again, as the surrounding tissue is infiltrated, its stroma becomes part of the stroma of the growth.

Bloodvessels and Lymph Vessels.—The bloodvessels and lymph channels of the host are retained by the growing tumor, by which means the tumor is nourished and gets rid of its excretions. As the tumor grows, the vessels also grow, but never beyond the stage of capillaries; there is never formation of muscular walls, or of arteries or veins proper, and even perfect vessels that become enclosed in a growth are simplified and lose their specialized characters. Thus it is evident that *a blastoma has no power of regulating its blood supply.*

Nerves.—The host supplies no nerves to the blastoma. A few fibres may be seen to pass into the periphery of a tumor, but they evidently quickly undergo destruction and absorption, and the deeper parts of the tumor are without nerves. There is thus no trophic or vasomotor control exerted on the tumor by the body, and the activities, vegetative and other, of the neoplasm can be influenced only through

the composition of the body fluids and by alterations in the resisting powers of the surrounding tissues.

Degenerative Changes.—Degeneration is very likely to occur in a neoplasm, especially since the tumor can to so small an extent control its own nutrition; apart from imperfect vessels the tumor cells have no other source of nourishment than the fluid of the surrounding tissues, and of this the peripheral cells of the neoplasm obtain the best and most, leaving the centrally situated parts badly off for food and oxygen. Not only this, but the peripheral cells may get rid of their products by diffusion into the surrounding tissues, whereas the central cells must "stew in their own juice," and be damaged or killed thereby. Necrosis and absorption of the deep-lying parts of an internal neoplasm, and of the most superficial part of a superficial tumor, are, therefore, liable to occur; and the bloodvessel walls being thin and exposed also to the same deleterious influences, are liable to rupture and permit hemorrhage.

FIG. 139
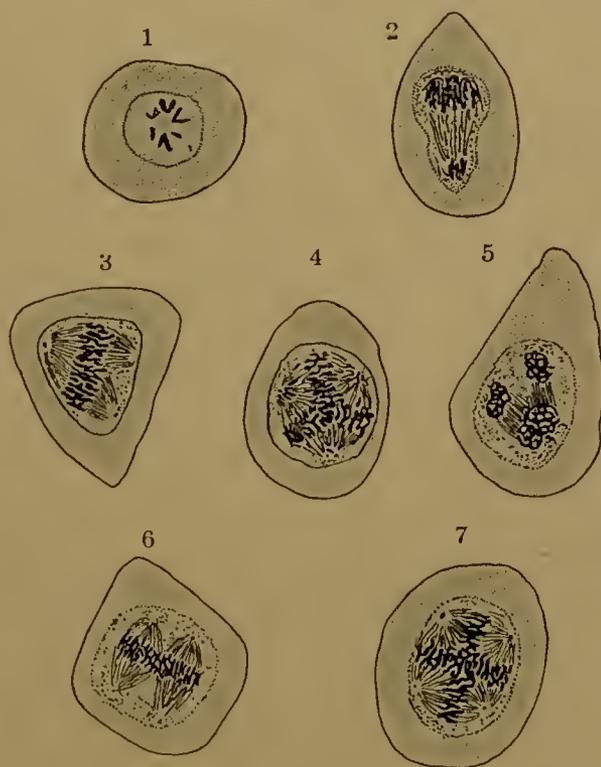
Irregular mitoses in cancer cells: 1, hypochromatic mitosis; 2, asymmetric mitosis, the upper daughter nucleus hyperchromatic; 3 to 7, various forms of multipolar mitoses. (Galeotti.)

Nuclear Changes.—Much work has been done in the observation of the process of mitosis in neoplasms, and while no rules have resulted by which we can determine the degree of malignancy possessed by a given tumor, yet many strange deviations from normal have been observed. The mitotic process is at times hypochromatic (that is, the number of chromosomes is reduced below that normal for the species), at times hyperchromatic (the opposite of the former), or pluripolar, in which there are more than two centrosomes, each centrosome attracting chromosomes so that multiple nuclei may be produced.

Retrogression and Healing.—It is by the help of these degenerative changes that retrogression, and even disappearance and absorption of tumors occur, although this result is an unusual one. Many cases of disappearance of tumors, even the most malignant, have been reported, and it is upon this possibility that we can base hope of attaining ultimately a means of cure; even now we know certain means that have met with a measure of success, such as the use of arsenic and salts of selenium and tellurium; of Coley's inoculation fluid of sterilized cultures of streptococcus and B. prodigiosus (based on the experience that intercurrent erysipelas may lead to the absorption of malignant growths); of extirpation of the ovaries in mammary carcinoma; of electropuncture in uterine myomas; and of ultraviolet and the Röntgen rays upon superficial growths.

Classification of the Autochthonous Blastomas.—It may be here repeated that the autochthonous blastomas are neoplasms which arise in a body by proliferation of cells belonging to that body; this is to distinguish them from **heterochthonous (teratogenous) blastomas** which arise in a body from cells belonging to another individual. There is perhaps no word in the language which conveys precisely this meaning and we are compelled to use this clumsy term. In devising a classification it is necessary to remember that finality of knowledge of tumors is far from being attained, and it would be unwise to attempt to claim finality for any classification made at the present day; the intention is to construct a working classification along the lines of the origin of the various tissues affected, that is, an embryogenetic classification, and this because our microscopic diagnosis is dependent upon cell characters.

This is not the place to deal particularly with already existent classifications.

Each tissue in the body has a definite origin and mode of development, and if neoplasms are derived from definite tissues, and their component cells represent stages in the development or the retrogression of these tissues, it becomes necessary to distinguish and possible to classify tumors according to the tissue from which the neoplasm springs. Considering the earliest stage that has been recognized in the development of the fertilized ovum after it has begun to segment, that is, the **morula**, we have merely a cluster of undifferentiated cells. Rapidly these cells arrange themselves into two layers, the **epiblast** and **hypoblast.** Between these the hypoblast and, to a less extent, the epiblast give rise to a poorly differentiated mass of cells hardly to be called a layer, the **mesoblast.** The reader must correct the old idea that connective tissues and connective tissues only arise from mesoblast; and that epithelium and glands and nerves, and these alone, from epiblast and hypoblast. From the epiblast, for example, there is developed along the dorsal groove a mass of cells of which those away from the surface are no longer stratified. As the dorsal groove becomes infolded this portion becomes cut off from the rest, the only

part recalling the original epiblast being the ependymal layer around the central canal, these cells having originally been outer layers of the dorsal groove. A similar ingrowth of cells occurs from the hypoblast to form the notochord. We find that these ingrowths from the epiblast and the hypoblast come into most intimate relationship subsequently with mesoblastic structures. The mesoblast in its turn

Fig. 140

MESENCHYME
(*hylic*)

EPIBLAST
(*lepidic*)

EPIBLAST
(*hylic*)

MESOTHELIAL
SKELET-MUSCLE
(*hylic*)

NOTOCHORD
HYPOBLAST
(*hylic*)

ENDOTHELIUM
(*lepidic*)

MESOTHELIUM
(*lepidic*)

PLEURO-PERITONEAL
CAVITY

LOMEN·OF ALIMENTARY
CANAL

HYPOPLAST
(*lepidic*)
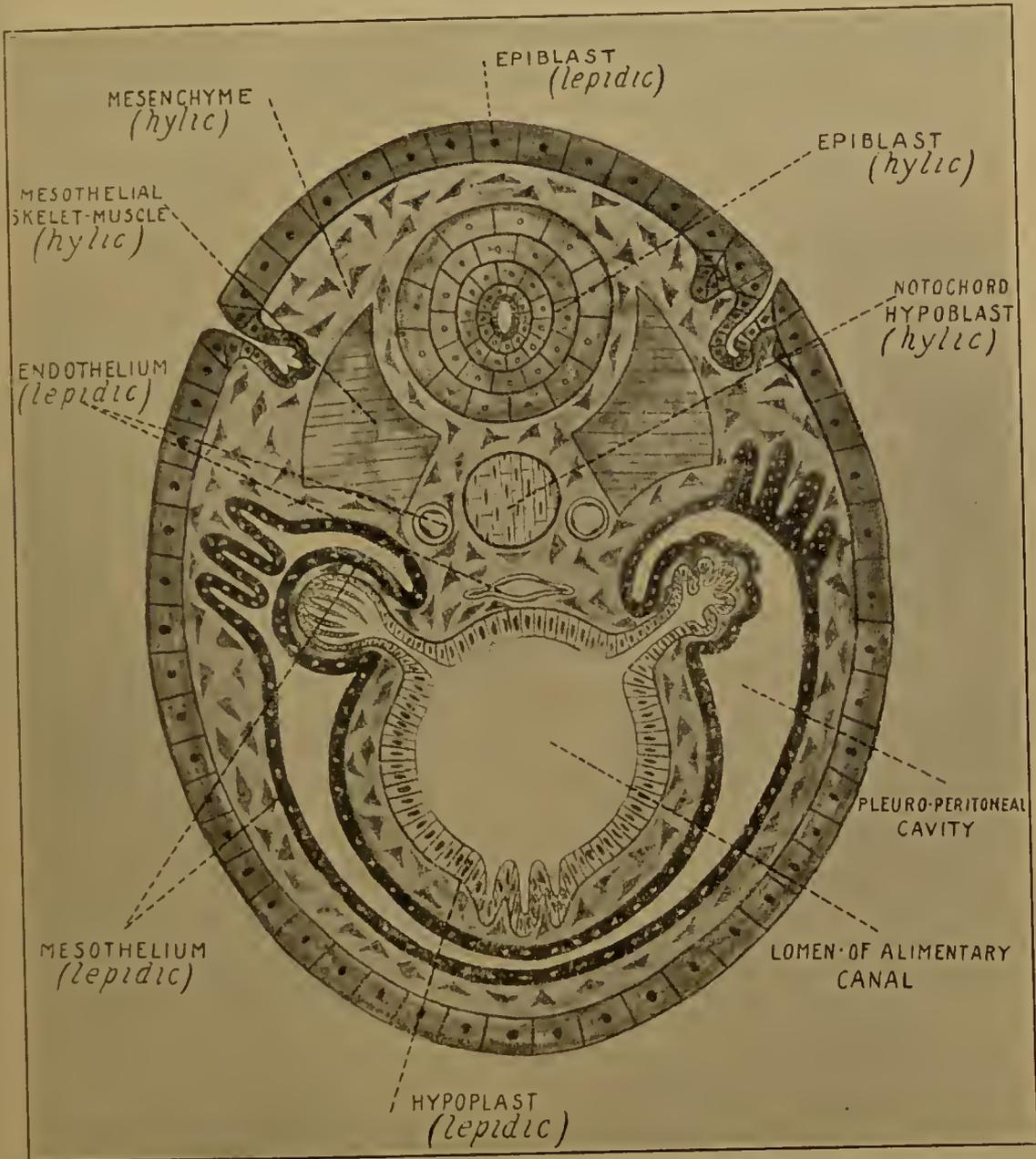
Diagrammatic representation of section through vertebrate body to show ontogenetic relationship of the various orders of tissues.

undergoes changes; when it splits to give origin to what will ultimately be the primitive body cavity, or cœlom, the cells lining that cavity become arranged in a layer, the **mesothelium**: the remaining part of the mesoblast, which does not become so differentiated, constituting the **mesenchyme**. From the mesothelium again, there occur ingrowths into the mesenchyme which are comparable to the ingrowths from the

epiblast and hypoblast; these are the **myotomes**, the *anlagen* of the future striated muscles of the body. Further, a mass of mesenchyme which will ultimately be recognizable as the heart and trunk vessels is seen to develop a central cavity, and the mesenchyme cells lying upon this cavity become differentiated into a definite layer, the **endothelium**. We thus find that the embryo becomes divisible into collections of two orders, which may be termed "lining membranes" and (for lack of a more expressive word) "pulps," the lining membranes being persistent epiblastic, hypoblastic, mesothelial, and endothelial layers, the pulp being the main mass of the neuroblast (of epiblastic origin), the notochord (of hypoblastic), and the mesenchyme (of mesoblastic). Briefly expressed, each layer in the original embryo becomes differ-

FIG. 141

FIG. 142
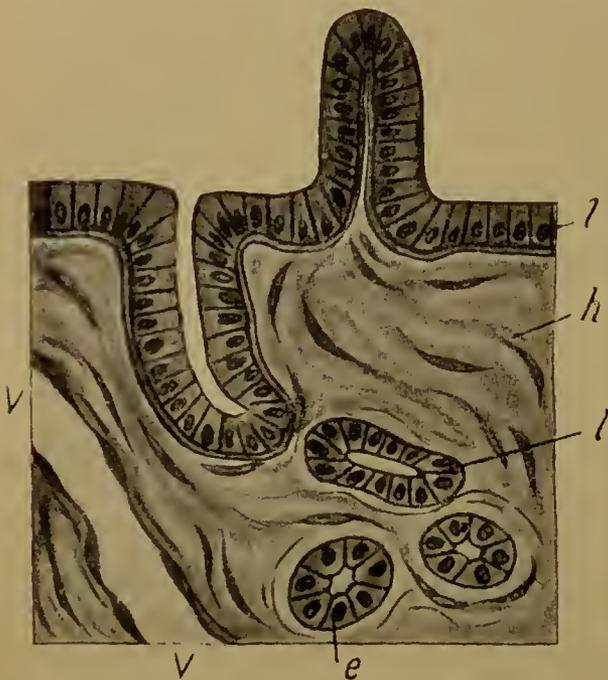
Diagram of typical lepidic tissue. The specific tissue cells form connected series in apposition. Their nourishment is gained from the vessels (*v*) and lymphatics of the underlying hylic supportive tissue. *l, l*, the specific cells of the tissue; *h*, the underlying stromæ, with a vessel, *v*. The vessel is lined by a simple lepidic endothelium.
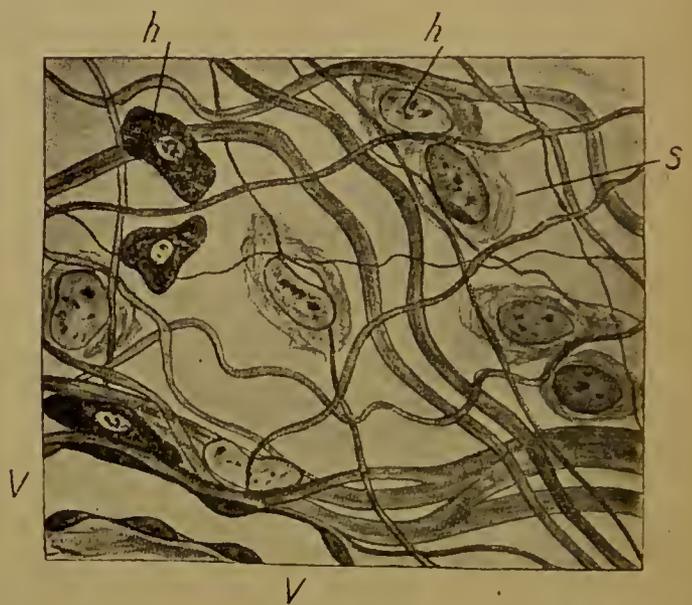
Diagram of typical hylic tissue. The specific tissue cells lie in a stroma, with intervening lymph spaces and channels, and bloodvessels. *h, h*, the specific tissue cells; *s*, stroma, interstitial, with fibrils, lymph spaces, etc., between the individual cells.

entiated into lining membranes and pulps. To the former we apply the term "**lepidic**," (from λεπις, a rind or skin), and to the latter "**hylic**" (from ὕλη, crude material), both words being used as adjectives.

The characteristic of the lepidic tissues is that the cells are arranged in layers or clusters in *direct apposition; they are not separated by lymph or blood vessels*, and they possess a supporting framework or stroma of hylic tissue in which run the nutrient vessels. The features of hylic tissues are the opposite; *separating the cells there is a matrix of intercellular substance*, either homogeneous or fibrillated, while *lymph spaces and vessels and blood capillaries tend to separate and run between the*

individual cells. If in the lepidic tissues there is a stroma of hylic tissues, so in the hylic tissues there is lepidic tissue in the shape of the endothelium of the blood and lymph vessels, in each case the elements of the other order being subordinate.

On this basis we obtain the following classification of normal tissues:

I. **Lining Membrane or Lepidic Tissues**, in which the bloodvessels do not penetrate the groups of specific cells and in which there is an absence of definite stroma between the individual cells, although such

FIG. 143
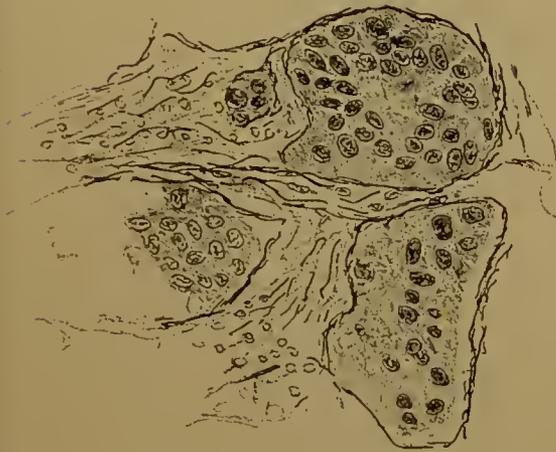
FIG. 144

Section of carcinoma simplex of breast, treated with Mallory's connective-tissue stain, to demonstrate a complete absence of passage of intercellular fibrils between the individual members of the alveolar cell groups. (Woolley.)

Section of an endothelioma similarly treated. The alveolus below reacts almost wholly like an epithelial cancer, that above exhibits intercellular connective-tissue fibrils, like a sarcoma. (Woolley.)

stroma, of mesenchymatous origin, may be present between the groups of cells:

1. *Epiblastic:* Epidermis. On this basis we can classify the normal tissues of the body into lepidic and hylic respectively. I. We observe that lepidic tissues may be of various origins, (1) some *epiblastic* (epidermis and epidermal appendages, mucous membrane of nose, etc., anus, most of male urethra); (2) some *hypoblastic* (mucous membrane of digestive tract and specific cells of associated glands, liver, pancreas, etc., of the bladder and prostatic portion of the male urethra); (3) some *mesothelial* (serous membranes of pleura, peritoneum, etc., and specific cells of adrenals, cortex of kidney, testes, ovaries, etc.), and (4) some *endothelial* (endothelium of bloodvessels and lymph channels). II. Similarly,

hylic tissues may be of diverse origins: (1) *epiblastic, e. g.,* nerve cells and neuroglia; (2) *hypoblastic*—the notochord; (3) *mesenchymatous* (the various connective-tissues, reticulum of lymph glands, bone marrow, plain muscle tissue, blood corpuscles); and (4) *mesothelial* (striated muscle, including cardiac muscle.

Now as originating from those various tissues blastomas may present either predominating lepidic or hylic characters. We could divide them into lepidomas and hylomas. As a matter of fact, we have already made this distinction among malignant growths, when for the last two generations we have made a sharp distinction between **carcinomas** and **sarcomas.** These two terms, it seems to us, can only be retained if we give them a purely morphological significance, and keep in mind that any lepidic tissue, whatever its embryogeny, can give origin to a carcinoma; any hylic tissue give origin to a sarcoma.

We have suggested elsewhere that the reason why certain tumors of certain tissues at times, when growing slowly, present the lepidic structure, at other times rapidly, the hylics, while other examples exhibit both types of structure is this, that they originate from tissues which in their development were the last to assume the lepidic type, which consequently lose this characteristic the most easily. This is the principle that the earliest acquirements are the last to be lost, the latest are lost the soonest. It is the mesotheliomas and endotheliomas (tumors originating from mesothelial organs like the adrenals and kidneys and from the endothelium of blood and lymph vessels), that most often exhibit the mixture of carcinomatous and sarcomatous characters.

It may be laid down as a rule in all tumors that the more rapid the growth, the more do cells lose those features that were formerly specific to them as the constituent cells of this or the other tissue; the individual cell may thus afford little or no clue to the tissue of origin, but by the general arrangement of cells it is possible to see at least resemblances to connective tissues or to glandular tissues, and thereby to know what kind of tissue gave origin to the tumor. We note, in any case, a reversion to a simpler, earlier, more "embryonic" type of tissue, in which proliferative or vegetative activity has replaced functional activity and caused the tissue to lose those features that are distinctively connected with the performance of function. With this loss of power to perform its function, we believe the tissue to be incapable of regaining the same; a hylic tumor, being composed of tissues of less specialized type.

HYPERBLASTOSIS

Before passing in review the different orders of tumors, it is necessary that attention be called to a condition usually included among the true tumors, which, however, is an intermediate condition, on the one hand having characters in common with the true hypertrophies, on the other having manifestations indistinguishable from the blastomas proper.

We have already referred to the diffuse overgrowth of individual tissues which is apt to accompany disturbances of function of certain organs affording an internal secretion—to the myxœdema and overgrowth of connective tissue associated with arrested action or atrophy of the thyroid, the overgrowth of the organs of generation, and of the muscular system seen in some cases of overgrowth of the adrenal cortex, and we may add, recorded also in cases of pineal disturbance. Allied with these is an interesting group of cases in which the fatty tissue of one or other region of the body—of the neck or trunk, the mesentery

Fig. 145

Multiple fibromatoid overgrowths along the course of the cutaneous nerves. (Herczel.)

or retroperitoneal or circumrenal regions—undergoes a huge hypertrophy. Sometimes this is diffuse as in typical examples of Dereum's disease (adiposis dolorosa) sometimes nodular although multiple. The condition is spoken of as liposis, adiposis, lipomatosis, and often as lipoma. The interesting fact is that in extreme cases of Dercum's disease, relief and disappearance of the fatty accumulation is brought about by subjecting the patient to thyroid medication. Evidently we deal here with a metabolic disorder leading to an abnormal accumu-

lation of fat in one or other region of the body. What we would emphasize is that not all the regions of fat deposit are affected equally in these cases, and that sometimes the growths take on the appearance of isolated well-defined tumor masses, so resembling true blastomas; what is more, sometimes they take on active malignant growth in one or other area. Now we encounter similar general overgrowths of other tissues, presenting the same liability to affect specially certain regions. What their cause is we do not know: they have so many features in common with the last case that apparently they belong to the same category. A striking example is the condition known as multiple fibroma, fibroma molluscum, Recklinghausen's disease, fibromatosis, neurofibromatosis, or neurinomatosis (Fig. 145). It is a condition in which progressively more and more tumors appear specially in the subcutaneous regions, and along the course of the nerves. In extreme cases there may be hundreds of these tumors or nodes beneath the skin, varying in size from that of a pinhead to some three or four inches across, and causing great deformity. At first regarded as multiple fibroid tumors, further study showed the constant presence of axis-cylinders and medullated nerves in the masses. Now the demonstration appears complete, that the main element in the growths is a proliferation of the cells of the sheath of Schwann—cells of the same origin as the glial cells. In fact the neuroglia of the brain and spinal cord shows at times a like tendency to patches of ill-defined overgrowth (gliosis). Most of the conditions labelled as glioma are, in our experience, of this same order. Both of the conditions, while apt to be present for years, may take on eventually malignant characters.

Of most importance, clinically, is the group of conditions which we have been accustomed to label as myelogenous and lymphatic leukemia, chloroma and multiple myeloma. In all of these we deal with not a single focus of new growth, nor on the other hand a universal involvement of the lymphoid or bone-marrow tissue, but with a hyperplasia involving several areas—several groups of lymph nodes simultaneously, the whole spleen, the medulla of one or several bones. The causation of the conditions is completely unknown. At first we deal with what appears to be a simple hyperplasia of one or other tissue element of the lymphoid group, without any tendency to invade or pass beyond the natural boundaries of the past: there may, in fact, be nothing beyond an excessive growth: but often here or there in some affected region we obtain evidence of malignancy and infiltration of neighboring tissues. We have, in short, conditions of *lymphadenosis* or *myelosis*, terms which should replace the older *leukemia;* for "leukemia," the appearance of leukocytes in the blood, is not an essential part of the disorders: it is Hibernian to speak of a leukemic leukemia, or the preleukemic stage of leukemia. It is more intelligible to refer to lymphadenosis (or myelosis, with—or without—leukemia.

The Main Orders of Blastomas.—Before dealing with the large question of causation we will pass in review the various forms of

autochthonous blastomas or, in plain language, of the tumors more commonly encountered, beginning with the simpler, those of hylic type. We would here emphasize that by a blastoma we mean *an independent growth of cells of one or other order of tissue, apparently a cell colony or republic growing independently of the nervous control and the needs of the host individual.*

TYPICAL HYLIC TUMORS

Fibroma.—The fibroma is a typical tumor of fibrous connective tissue; typical, in that the copy (the tumor) is a good imitation of the original (the fibrous connective tissue). The original tissue lies widely scattered throughout the body, so that such a tumor may arise in many situations. Just as connective tissue varies in its composition, being in some regions loose and areolar, with relatively frequent cells, and in others, dense and firm, with relatively few cells, which are necessarily compressed, so the tumors vary, and we have **soft** and **hard** fibromas from these tissues respectively; the soft arise, for example, from subcutaneous tissue, the hard from dense tissues such as tendons, fasciæ, and periosteum. All alike, however, are composed of connective-tissue cells, connective-tissue fibrils, some elastic tissue, and blood vessels. Lymph spaces are seen in greater or less prominence according to whether it be a soft or a hard fibroma. The fibroma generally forms a well-defined nodule which grows slowly, and presses upon and replaces the tissues near it; if there be rapid growth, however, the cells, instead of resembling fully developed connective-tissue cells, are like fibroblasts. The greater the tendency to resemble fibroblasts, and the less differentiation there is in the direction of perfection of the connective-tissue cells, the more does such a growth approach in structure a sarcoma; the only sure differentiation between the benign and the malignant (sarcomatous) growth is the absence or presence of infiltration, and invasion of surrounding tissues. Lest one should be misled it is well to remember that all fibromas are more cellular than is normal adult connective tissue, and the growth of a fibroma of the most innocent kind occurs by the proliferation of such fibroblasts, and not of fully formed connective tissue.

The fibroma is pale on section, and the firmer ones are glistening, with an appearance that recalls watered silk; this is due to the bands of fibres that run in all varying directions, each band being originally laid down parallel to or around a blood vessel. A section through the tumor will show some bands cut transversely, others longitudinally, and others obliquely. In the gross, the fibroma is generally sharply circumscribed, and can readily be enucleated, but the sharp boundary line cannot be so well seen under the microscope, because the surrounding tissue is of the same order, and the normal and tumor tissues pass readily into one another.

Degenerative changes are prone to occur in fibromas, and by arrest of blood supply, or by tension they undergo necrosis, and in the necrosed area is much cholesterin and fatty material, which subsequently may become converted into calcareous nodules. If the lymph outlets be obstructed, the tumor may become œdematous, lymphangiectatic, cystic, or mucoid.

In certain situations, as in the mammary gland, a fibroma may be found to have in its midst glandular elements; this probably means that an inflammatory fibrosis has taken on tumor formation, and the localized fibroma thus formed has included glands that were originally normal; such a tumor is a pure fibroma, and not a fibro-adenoma; it is a **fibro-adenoma** only when there is a proliferation of the included glandular elements. As a matter of fact, there is a good deal of looseness in our use of the term fibro-adenoma; some of these are pure fibromas

Fig. 146
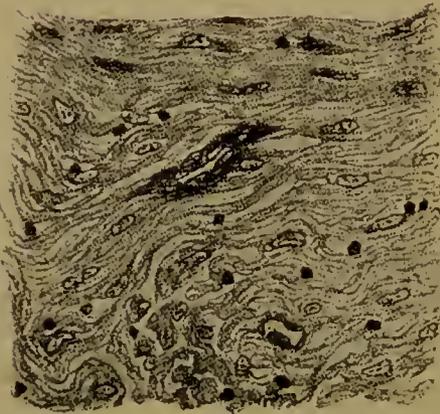
Hard fibroma.   (Ribbert.)

Fig. 147

Soft fibroma.

with gland tissue included, and others are not actually true fibromas at all, because the fibrous tissue is not circumscribed (blastoma), but is general, and diffuse, of the nature of hyperblastosis (See p. 344). True fibromas do not form metastases and do not recur after removal; if recurrence does happen, it means either that the growth was originally sarcomatous or was hyperblastoid, in which latter case the recurrence is simply the expression, once more, of the diffuse overgrowth which was originally wholly or partly removed.

Hard Fibromas.—Hard fibromas are found in many different situations but most often in connection with tendons or fasciæ; this rule is not absolute, for we find them in soft tissues such as the kidney. A variety occurring in connection with the jaw is **epulis**, a term often improperly given to osteoid and osteosarcomatous growths in this situation; it develops from the periosteum in connection with the root of a decayed tooth. Uterine fibromas and "fibroids" will be discussed with the myomas of that organ.

Soft Fibromas.—These are frequently multiple, and many of them are hyperblastoid. They are most frequent in the skin, pharynx, and digestive tract, and those in the nose and throat are apt to be soft masses—mucoid polyps—of the true myxofibromatous type.

Cheloid.[1]—Although distinct in its etiology, and somewhat in its histology, cheloid may be confused with the true fibroma. It consists in an excessive development of subcutaneous fibrous connective tissue, sometimes so great as to produce large overlapping masses of new growth covered by stretched skin. Two factors are present in its occurrence: (1) a congenital predisposition, and (2) irritation or injury. It is especially common in negroes, and in those who suffer from it, a slight cutaneous injury is liable to be followed by its development. In a

Fig. 148

Fig. 149

Section from a growth in a case of cheloid to show the coarse, hyaline connective-tissue bundles. (After Ribbert.)

Masses of cheloid at angle of mouth, at angle of each jaw, and on chest. (Todd and Wolbach, Gambia Expedition.)

case studied in our own laboratory, the mere running of a pin point along the forearm with a force sufficient to cause reddening but not bleeding, was followed by the development of little fibroid nodules along the track of the pin. Although some cases are spoken of as spontaneous, it is probable that in all cases it follows irritation, even so slight as the pressure of a shirt stud on the skin.

Microscopically, there is no capsule and the overgrown scar passes imperceptibly into the normal connective tissue. The fibrous tissue of the cheloid often shows thick, homogeneous bundles or strands of a hyaline appearance, between which lie fibroblast-like cells; elastic tissue is absent.

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[1] Some authorities write this keloid, from κηλίς, a crab's claw (from the cancer-like way in which the processes spread into the surrounding corium); others cheloid, from χηλη, a scar (from the relation of the growth to scar tissue). The latter is the less fanciful derivation.

Unlike the fibroma proper cheloid is liable to spontaneous absorption, and steady pressure may be followed by disappearance.

Myxoma.—Some pathologists doubt whether we ought to regard the myxoma as a tumor, and consider that we should speak of myxomatous degeneration of some one of the various forms of connective-tissue neoplasm — of lipoma, chondroma, or fibroma —using the term **lipoma myxomatodes** rather than *myxolipoma*, etc. This is, to a great extent, true but pure myxomas of the endocardium have been described, and myxomas are sometimes recognizable at birth. The mucoid nasal polyps, so frequently called myxomas, follow chronic inflammation of the nose, and are often not mucin-containing, but merely œdematous; as soon as the œdema is sufficient to weigh down the mass of inflammatory tissue, its draining is prevented, and the condition becomes progressive, the œdema cumulative. Some few, even nasal polyps are, however, mucin containing.

FIG. 150

Section from typical portion of a mucoid polyp. (Collection of Royal Victoria Hospital.)

The tissue which the myxoma most resembles is not to be found in the adult body, but is the tissue of the umbilical cord known as Wharton's jelly, and the developing subcutaneous fatty tissue of the fœtus. In pathological states, we find, in the regions around inflammatory areas, fibroblasts lying in a mucinous matrix; we realize, in fact, that mucin, which is a "low-grade" protein, has some obscure connection with the development of fibrous tissue, and we recognize a connection with this development not only in the localized myxoma, but in the generalized mucinous condition called myxœdema.

A true myxoma is composed of isolated stellate cells, or polyhedral cells with processes (the so-called "spider cells"), which are separated from one another by a mucin-containing matrix, the mucin taking a differential stain with thionin. In the matrix run large, thin-walled vessels.

The tumor is slowly growing, soft, and fluctuating, so as to seem at times cystic. It forms no metastases; a certain number of myxomas do become sarcomatous, and when they do the metastases are purely sarcomatous, and show no myxomatous characters.

Lipoma.—The lipomas are sharply defined tumors composed of fatty tissue; even if situated in the midst of fat there is no difficulty in recognizing the tumor, even if its color be not paler than the surrounding fat, as it often is; there exists some difference between normal fat and the fat of a lipoma, for where a large lipoma is present the body

may progressively emaciate and yet the fat of the lipoma will not be taken to supply the bodily needs. The lipomas are usually single but may be multiple, and vary in size from the very minute ones observed in the kidney to the 63-pound retroperitoneal mass around the kidney which, as will be pointed out later, comes properly under the condition of hyperblastosis (p. 344). Generally rounded, they may have finger-like processes radiating into surrounding tissues. They grow slowly and do not recur after extirpation. Modifications may occur, such as that part of the tumor becomes jelly-like and mucinous, the *lipoma myxomatodes;* an unchanged lipoma may even be so fluctuant as to be taken for a localized collection of fluid; at times a kind of necrosis is followed by the development of oil-containing cysts; cartilage and even bone have been found in lipomas, a phenomenon which is probably to be accounted for by metaplasia.

Most frequently the lipoma is subcutaneous, especially in the region of the shoulder and arm; a curious clinical fact is that one of these tumors under the influence of gravity may change its position and lie, for example, lower down upon the arm than was at first the case. Internally, they occur in the submucosa of the intestine, in the kidney, in the brain, in the omentum, and as enlarged appendices epiploicæ; lipomatous processes may develop in connection with the joints, projecting into the synovial cavity, as in the knee.

Xanthoma.—The xanthoma is a small, benign, fatty tumor of a yellow color, subcutaneous, sometimes multiple (**X. multiplex**), often found near the inner canthus of the eye (**X. palpebrarum**). Formed of connective tissue, it contains yellow fatty globules, in which the pigment is of the nature of a lipochrome. It is probable that the xanthoma is not a tumor but a fatty or lipochrome degeneration of tissue. The multiple form is found associated with diabetes (**X. diabeticorum**).

Chondroma.—Chondromas are tumors of cartilage, hyaline (**hyalo-enchondroma**), fibrous (**fibro-enchondroma**), or reticulated (**reticulated enchondroma**). They may be single or multiple, and in general have a distinct fibrous capsule. There are two varieties, the ecchondroma, and the enchondroma, of which the former is an outgrowth of cartilage where such is normally present, as in the costal cartilages, the larynx, the trachea, and elsewhere; they are truly local hypertrophies, and are to be considered as hyperblastoses. In the chondroma proper, or enchondroma, we have to deal with a mass of cartilage having no connection with a parent matrix. Such occur in many regions, notably in connection with the bones, the parotid, the submaxillary glands, the testes, the mammary glands, the lungs, and more rarely in the ovaries, the corpora cavernosa, and other organs. They do not arise from the cartilages of joints, although they may develop in the fringes of the synovial membranes, forming the "loose cartilages" of joints.

As in normal cartilage, few or no bloodvessels are found in the

substance of the tumor, and for this reason, if large, the mass is lobulated, the intervening connective tissue carrying the bloodvessels. In the large growths, the deeper parts give place to bone (**osteo-enchondroma**), or calcareous infiltration occurs (**enchondroma petrificum**). There is also considerable tendency to central necrosis, and if a necrotic area opens to the exterior it is apt to be very intractable, and even to give rise to general sepsis. Occurring in the parotid and testes, the chondromatous formation is part of a teratoma. Mucinous change occurs frequently, the tissue becoming so perfectly transformed as to justify the use of the term myxo-enchondroma.

Benign and slowly growing as these tumors are, nevertheless they may form metastases; nor is this only in the case of those mixed tumors where there is more than a suspicion of sarcoma, for metastatic enchondromas may show absolutely no malignant characters. We have here an example of a benign tumor showing one of the most characteristic

Fig. 152
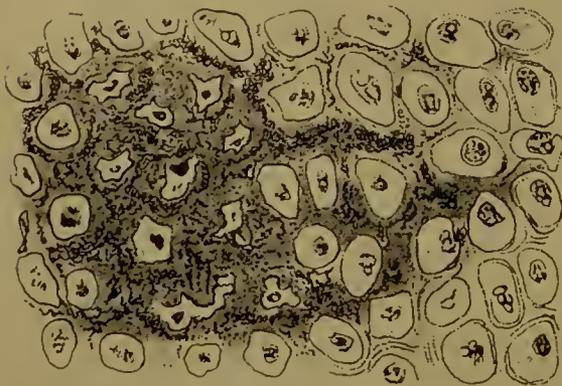
Fig. 151

Enchondroma exhibiting calcareous infiltration (*E. petrificum*). (Ribbert.)
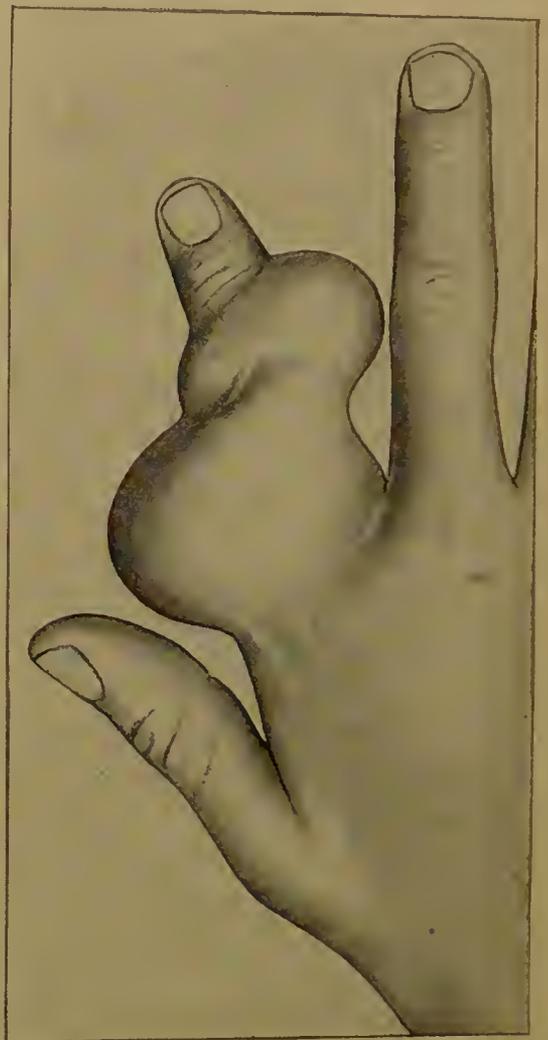
Ecchondroma of finger. (Shepherd.)

features of malignancy, and the explanation is a difficult one; it may lie in the high grade of vegetative activity possessed by the superficial chondroblasts which become free in the blood stream, and are carried elsewhere.

Without undertaking to discuss the etiology of these tumors, it may be said that they are prone to develop in early life, especially those occurring in bones, and there they are often connected with rickets, a disease in which there is undue preparation for the formation of cartilaginous bone, and a tardy formation of the same. In the region

of the epiphyses, this excess of cartilage projects into what is destined to be the shaft of the bone, and pieces become isolated which may give origin to enchondromas or osteomas. In some parts of the body, there is a fair likelihood that "rests" form the source of origin of these tumors; for example, chondromas in the parotid may arise from the cartilaginous remains of the hyoid arch, and those of the mammary gland from included parts of the sternal cartilages, but it is more likely that metaplasia of connective-tissue cells is the cause. Many cases of enchondroma furnish instances of trauma being a preceding factor.

Osteoma.—Osteomas, defined as tumors having a growth of their own, independent of the tissue in which they exist, are rare. Osteomatoid conditions, due to a regional hyperblastosis and connected with previously existent bone, are very common. A metaplastic formation of bone in another tissue, whose ramifications alternate with the ramifications of that tissue, is not a tumor proper, but nevertheless occurs frequently, and after dealing with the tumors we shall cite some of the numerous examples of this process.

The true osteoma may occur in connection with pre-existing bone (homoplastic), or apart from it in other tissues (heteroplastic). In the former case it may be superficial, derived from the periosteum, or may be within the bony substance (endosteal), and then originating either from (a) a misplaced piece of epiphyseal cartilage, or (b) from the bone marrow, in which case it exhibits no cartilaginous fore stage. It may be dense and hard or spongy and soft, but in any case it does not merge imperceptibly into the surrounding bone, so that it leads to absorption and weakening of the host bone.

Of heteroplastic osteomas, the simplest type is the isolated tumor arising from displaced periosteum in the neighborhood of a bone; this often shows no cartilaginous fore stage. Ossifying chondroma serves as a further example of the heteroplastic form.

Osteomatoid.—This, as was stated above, includes all cases of localized or general overgrowth of bones in which the growth is not defined from the normal bone, is not independent, and is of unknown cause (save, perhaps, that heredity plays a part).

Such are:

1. *Idiopathic hyperplasias* affecting one or several bones, especially the long bones.

2. *Enostoses*, localized and circumscribed growths within bones, not independent of the surrounding bone.

3. *Exostoses*, processes of various grades arising from the surface of a bone, not of traumatic origin. The ivory exostosis of the skull, or the ossifying ecchondroses at the ends of long bones serve as examples. It is difficult to separate from these, conditions such as myositis ossificans, in which bone gradually replaces set after set of muscles. This last should perhaps be considered as an example of the following.

Metaplastic Ossification.—This is an alteration of some part to bone, accompanying inflammation or senile changes in a tissue; examples

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are: (1) the "riders' bone," where bone is laid down in the adductor muscles of cavalrymen, from repeated trauma of the muscle; (2) the like case in the deltoid of the infantryman, from pressure of the rifle; (3) in the choroid; (4) in the pia, after inflammation; (5) the bony plates developed in the dura are even better examples; (6) in the heart valves and arteries; (7) in the lungs; (8) in old pleural and pericardial exudates, where bone formation often follows calcareous infiltration; (9) in various tumors—lipoma, fibroma, etc.

Odontoma.—Pure odontomas are rare, and odontomatoid conditions commoner, the growth not being independent of the cement substance, of the dentine or the alveolar periosteum of the tooth.

Bone-marrow Tumors.—The different elements in the bone marrow are these: on the one hand the cells directly concerned with the bone— the osteoblasts and the osteoclasts (or myeloplaxes); on the other hand, the erythroblasts, megalocytes, myeloblasts, and lymphoblasts—the mother cells of red-blood corpuscles and leukocytes. The cells of these

Fig. 153
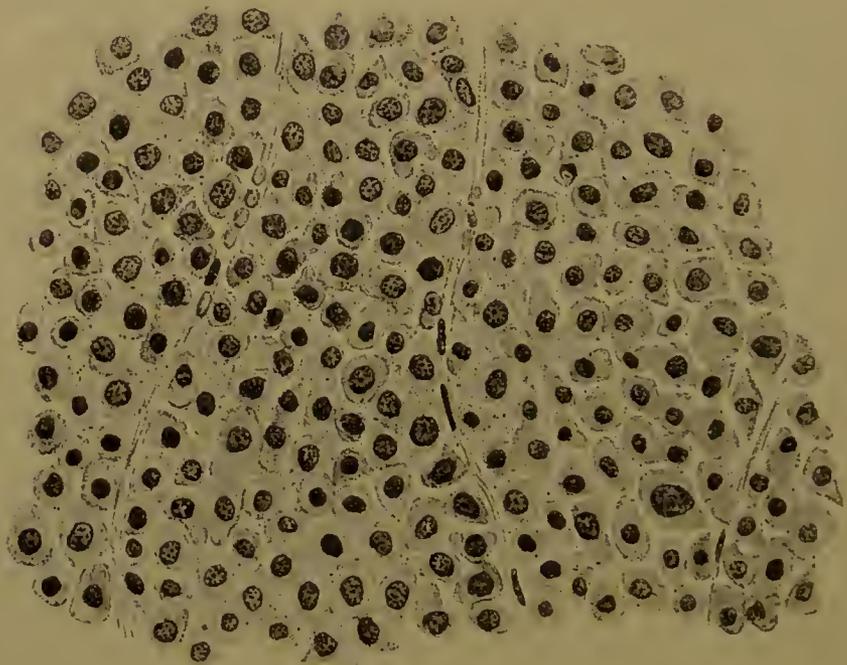
Section of myeloma of vertebra. × 600. (S. Saltykow.)

two orders, widely divergent in kind and in function, can give rise to corresponding tumors, and not only this, but each kind of cell can give rise to its own overgrowth. If we realize this, and apply the principle that each kind of tissue can give origin to three orders of growths, viz., (1) hyperblastosis, (2) typical blastomas, (3) atypical blastomas, diffuse overgrowth, we can reduce the various overgrowths of bone marrow to some show of order.

TYPICAL BLASTOMAS

The Gaint-celled Osteoblastoma (*"Giant-celled Sarcoma"*).—These grow locally, oftenest in the marrow of the long bones or of the jaw; they may be of periosteal origin, as in the giant-celled epulis of the jaw; they grow expansively, causing absorption of surrounding bone, are vascular and *do not form metastases*, save in the eases where sarcoma springs up in a hitherto benign growth; they do not reeur; nor do they require to be very "widely" removed. Histologically, the body of the tumor is formed of short spindle eells of fibroblast type, some- times polygonal, and giant cells are abundant. These giant eells are the "typieal" overgrowths of the myeloplaxes; bony spicules and lamellæ may grow in the tumor, although the more abundant the giant eells the less likely is bone formation to oceur. Finally, atypieal blastomatous growth (sareoma) may supervene in such a tumor.

ATYPICAL BLASTOMAS

These are, of eourse, the **sarcomas,** whieh may arise (*a*) primarily or (*b*) from typieal blastomas, such as the above, or (*c*) from hyper- blastoid overgrowth, sueh as the following:

Hyperblastoid Overgrowth.—Myelomatosis (*Myeloma Multiplex*).— This is a peculiar form of growth that affeets the red marrow of bones, such as the vertebræ, ribs or cranium, converting it into a dark red or reddish-gray, or grayish-yellow tumor mass. It is a primary multiple process, arising simultaneously in bones widely apart; at times the growths are soft and pulpy, at times firm; they may project up to and through the periosteum, and fraetures are thus eommon, or in the vertebræ, distortion. There is no sharp definition to the areas of hyperplasia. Yet with this progression the growth remains con- fined to the bones, and there are no metastases in lymph nodes or elsewhere. Clinieally, there may be fever, pain, and severe anemia, with albumosuria. Some of the names under whieh this remarkable eondi- tion has been known are malignant osteomyelitis, myelogenous pseudo- leukemia, sarcomatous osteitis, lymphadenia ossium; and our conten- tion is that even "myeloma" is ineorrect, in that it is a myelomatoid or condition of hyperblastosis.

Histologieally, there are the pure eases in whieh there is no over- growth of the myeloplaxes nor any indieation of the osteogenic ele- ments of the bone being implieated. The tumor cells are derived from the cytoblastie elements of the marrow, and are myeloblastie or lympho- blastic in type; this means that we may have loealized hyperblastoid over- growth of the lymphoblastie elements of the marrow without leukemia.

Myelosis with Leukemia (" **Myelogenous Leukemia**").—The eell growth in the above is local, but we have similar diffuse overgrowth of the bone marrow with abundant discharge of the eells into the eireulation.

Here there are in the blood great numbers of large mononuclear cells with neutrophile granulations, coupled with the presence of increased eosinophiles, "mast cells," and normoblasts. The ordinary red cells are reduced in number, the white cells greatly increased, and the myelocytes may be one-third or more of the total white cells. The bone marrow is seen to show hyperplasia, and is reddened. The main elements present are myelocytes, nucleated red cells, and numerous cells with eosinophilous granules. The great enlargement of the spleen is not primary, but is due to an accumulation of blood cells. Sometimes in the liver and kidneys there are tumors due to active growth of the myelocytes outside the capillaries; in fact, there is an overgrowth of the "leukoclastic" elements of the bone marrow, sometimes confined to their natural site and at times elsewhere in the body.

Chloroma.—This peculiar tumor, which is multiple, affecting the bones of the face, especially the orbit, the skull, the vertebræ, and more rarely the ribs and marrow, is characterized by a striking greenish or greenish-yellow tint, which fades as the specimens are kept; the pigment is said to be a lipochrome but this is not certain. The tumor is a medullary overgrowth, associated with which is a leukemia in which the prevailing cell is of the myeloblast type; evidently this is an aberrant form of **myelosis.**

Lymphoma and Lymphomatosis.—It would be unwise to plunge into the vortex of the numerous terms employed to describe the various lymphomatous states, and to lay down what seem to us the right interpretations of these various terms. We prefer to state: (1) that just as we recognize that the lymphocytes and the leukocytes (the polymorphonuclear and eosinophile cells) have distinct origins, so we have distinct series of blastomatous and hyperblastoid overgrowths originating from the tissues that give origin to these two orders of cells; (2) that just as among the overgrowths of fibroid tissue, there is a series of overgrowths from chronic inflammatory hyperplasia to typical fibroma and farther to atypical sarcoma, so here is an identical series. Now we can clear away the overgrowths of the "leukocyte-producing" tissues, as distinct from the "lymphocyte-producing" ones, and this we have already dealt with, since the leukocytes originate from the myeloblasts. The myeloblasts have their seat in the bone marrow; the marrow contains specific cells of different orders, viz., osteoblasts (and osteoclasts), and myeloblasts, along with other cells that are not specific—lymphocytes (lymphoblasts) and connective-tissue cells (fibroblasts). Growths derived from these specific cells are osteoblastomas (giant-cell sarcoma), myeloblastomas, myelosis with and without leukemia with aberrant forms of myelosis such as chloroma, myelogenous leukemia, and chloroma. This leaves us free to deal with the lymphoid overgrowths proper; and in doing this, to extend beyond the overgrowths of lymphoid tissue in the bones alone to those of lymphoid tissue in general.

1. **Chronic Hyperplasia** (comparable with chronic inflammatory fibrosis).—This is seen in connection with tuberculosis, where there

is a diffuse enlargement of lymph nodes, with or without caseation. This hyperplasia of the lymph cells present, even where bacilli are not demonstrable, is especially well shown in cattle.

2. **Hodgkin's Disease** (*Lymphogranulomatosis*).—Our views regarding this condition have undergone wide changes. At first included among the tumor growths, it was first recognized by Dorothy Reed, Longcope, and others as a chronic inflammatory disturbance of the lymph nodes; next Sternberg and other German authorities regarded it as due to the mild productive irritation set up by tubercle bacilli of low virulence. The latest view (Bunting) is that typical cases afford cultures of a diphtheroid bacillus, which in cultural properties differs from the B. tuberculosis.

The lymph-node groups of the body are successively enlarged, often beginning with the cervical, and finally, the spleen follows suit. There is diffuse lymphoid proliferation in areas where anatomically nodes are not described. The lungs remain free, and the blood shows no pro-nounced change. Histologically, the characters are different from those of leukemia; there are no signs of infiltration, as occurs in lympho-sarcoma; there is connective-tissue overgrowth, as occurs in the previous group, and a relative if not actual reduction in the lymphocytes and cells of the germ centres.

The same characters are found in the spleen, there being no excess of lymph cells noticed. But in areas where lymph cells are not normally prominent, there is great excess, the lymphocytes being laid down thickly around the vessels. These collections are provided with a reticulum of connective tissue, and do not infil-trate, though they may press upon and cause to atrophy the surround-ing tissues. We have, in fact, a *lymph hyperplasia and not a metastasis*.

The marked contrast between the

FIG. 154

Section of enlarged lymph node from case of Hodgkin's disease to show various orders of cell present, many of them of irritative or inflammatory type: *a*, large endothelial cell; *b*, fibroblast; *c*, eosinophile; *d*, occasional lymphocyte; *e*, polynuclear leukocyte. (Im-mersion lens.)

involved nodes and spleen on the one hand, and the secondarily in-volved organs on the other, strongly suggest that in the one we are dealing with reduction of the lymphoid elements, in the other with compensatory hyperplasia. It has been seen that in the early stages there is in the lymph nodes a similar lymph hyperplasia, followed by exhaustion or atrophy as the connective-tissue overgrowth progresses. The picture is thus not one of malignant growth. *Hodgkin's disease is not a form of lymphosarcoma or lymphomatosis.* It approaches much more nearly the results of chronic irritation; it may be compared with

cheloid and regarded as an overgrowth of the lymph tissues secondary to irritation.

3. **Lymphadenosis with Leukemia (Lymphatic Leukemia).**—There may be over-development of typical lymph tissue, the reticulum, the sinuses, and the cells being developed proportionately—a real hyperblastosis. At times this is restricted to the spleen or certain groups of lymph nodes, at times more widely developed, even affecting secondarily the liver and other organs. Of inflammatory overgrowth the indications are slight; the capsules of nodes may by distension be thickened, but the reticulum shows no corresponding overgrowth. The hyperplasia respects its boundaries and shows no signs of infiltration. This can exist without escape of the lymphocytes into the blood, a lymphadenosis without leukemia; only when an excess of lymphocytes appears in the circulation do we have true lymphatic or lymphocytic leukemia. It is conceivable that some cases go part of the way and then recede, there being, for example, a splenic tumor with temporary lymphocythemia which disappears.

4. **Lymphoma** (comparable with typical fibroma).—By analogy, we know that typical lymphoma exists, although reported cases are few; it is, of course, difficult to distinguish this from mere localized hyperplasia of a lymph node.

5. **Atypical Lymphoma; Lymphosarcoma.**—Since the lymph follicle contains tissues of more than one order, vessels and endothelium, along with the specific lymph cells, it is evident that there may be several forms of sarcoma originating from it—round celled, spindle celled, etc. Round-celled sarcomas of this order may be histologically indistinguishable from lymphosarcoma, and the cells of such a tumor may represent either a reversion from a differentiated connective tissue or else a lymphoma that has not greatly departed from the type of its original tissue.

6. **Lymphosarcomatosis.**—However widely a lymphosarcoma infiltrates the condition should not be called lymphosarcomatosis, because it is essentially by nature a localized growth. The term lymphosarcomatosis should be used to define a malignant, multiple, hyperblastoid overgrowth, of which cases have been described.

All these divisions, it will be seen, fall into three main classes: (1) productive lymphadenitis; (2) hyperblastosis (with and without leukemia); (3) lymphoma (typical and atypical).

Splenic Hyperblastosis (Splenomegaly).—Splenomegaly occurs under several clinical types. The splenic enlargement may be the only sign; there may be accompanying secondary anemia (splenic anemia), and cirrhosis of the liver (**Banti's Disease**), or it may be familial; or the splenic enlargement may be coupled with cyanosis and a great increase in erythroblasts in the splenic tissue and erythrocytes in the blood. These may number 10,000,000 per c.mm. In all these cases there is a local diffuse overgrowth of the spleen, and in the last, it seems as if the spleen reverted to its fœtal state, and became once more an active producer of erythrocytes. **Endothelial splenomegaly** (*Gaucher's type*) is a rare con-

dition in which general enlargement of the spleen is associated with a remarkable overgrowth of the endothelial cells lining the splenic sinuses, these sinuses becoming densely filled with large mononuclear cells.

Nothing is known about the causation of any of these diseases, though Banti has called attention to the fact that in the former condition

FIG. 155

Section of portion of a pure myoma, showing the character of the nuclei and the appearance of the cells cut longitudinally and transversely. (Perls.)

FIG. 156
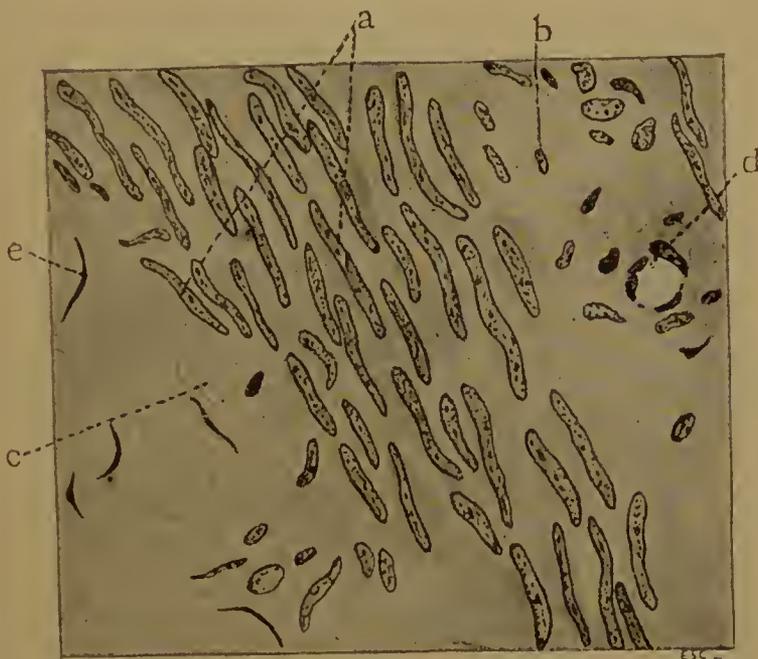
Section from a uterine fibromyoma (high magnification) to show: *a*, muscle cells with rod-like nuclei cut longitudinally; *b*, a bundle of muscle cells cut transversely; *c*, fibrous connective tissue around bundle, with (*e*) spindle-like nuclei of the same; *d*, a capillary.

there is evidence of active breaking down of the red corpuscles in the spleen, with accompanying anemia and icteroid state which may be recovered from completely when the spleen is extirpated.

Myoma (Leiomyoma).—The uterine fibromyoma or "fibroid," is the commonest of tumors. Very frequently they are multiple, existing sometimes in large numbers, and in situation (*a*) interstitial, (*b*) sub-

mucous, or (c) subserous; in the last two situations they may become pedunculate. The individual tumor is sharply defined, and some shell out easily while others are firmly anchored by a diffuse capsule. There are two general types and all stages of transition between them: (1) the pure myoma, reddish gray and softer than (2) the "fibroid" proper, almost white, and showing the watered-silk appearance on section. Variations and modifications occur, the following being seen: (1) telangiectatic tumors, in which the blood vessels are greatly dilated; (2) lymphangiectatic, in which the lymph channels are distended, leading sometimes to œdema, or to cyst formation; (3) occasionally, though rarely, hemorrhagic; (4) necrotic, an actual liquefaction at times occurring; at others, a red hemorrhagic necrosis recalling the red infarct; (5) calcified, so that the mass can be cut only by the saw, this state being preceded by fatty or hyaline degeneration.

Microscopically, all grades exist from pure myomas to what are almost pure fibromas. The beginner generally finds difficulty in dis-

Fig. 157
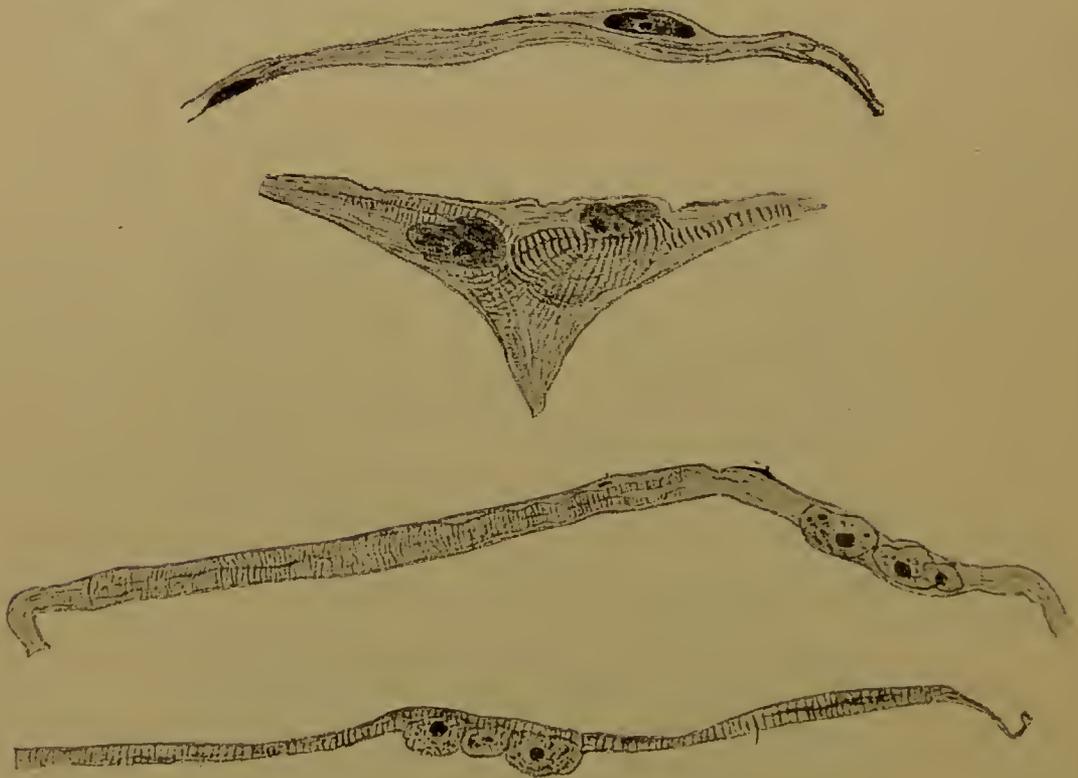
Imperfectly formed striated muscle fibres from a rhabdomyoma of the œsophagus. (Wolfensberger.)

tinguishing the two tissues, but if the nuclei be examined, it will be seen that those of connective tissue are short and spindle shaped, those of muscle larger, longer, rod-like, and with blunt rounded ends. Cut transversely, too, the connective-tissue nucleus has a naked appearance, while the muscle nucleus has around it a fair amount of cytoplasm. The small tumor is preponderatingly muscular, the larger fibroid, a change due to the fact that the relatively poor blood supply causes the gradual effacement of the higher tissue. These tumors are essentially benign, grow locally, and sometimes throughout a long period of years;

clinically, they are often associated with menorrhagia or metrorrhagia, they obstruct pregnancy, and the demand for their removal is by no means so negligible as their histological nature might suggest.

It is not possible, in the present condition of our knowledge, to offer any accurate supposition as to the etiology of these tumors.

"Adenomyomas."—These are diffuse not circumscribed myomas of the uterus containing scattered gland tubules that exhibit no sign of active growth. Although they have led to much debate there seems considerable reason to suppose that these glandular elements are merely inclusions of uterine glandular tissue, and the tumors not true adenomyomas.

Myomas of Other Regions.—The uterine myomas have been discussed because of their overwhelming frequency and importance compared with myomas elsewhere. The sites in which they are especially seen are: (1) other parts of the genito-urinary system, the Fallopian tube, the broad ligament, the testis, prostate, kidney, ureter, and mammary

Fig. 158

Cells from a benign and a malignant neurocytoma (or true neuroma), respectively, the former from the sacral region, the latter from the retroperitoneal region at the level of the pancreas. (R. Beneke.)

gland; (2) the digestive tract, especially the stomach and intestines; (3) the skin, where they are sometimes multiple, not associated with occurrence in other parts of the body. Whether they arise from the muscle of the arteries or the erector muscles of the hair follicles is debatable, but when the universal distribution of the artery muscle is considered it seems more likely that they arise from the latter.

Rhabdomyoma.—We now pass to hylic tumors of mesothelial origin. Neoplasms of striated muscle fibres are found usually combined with growths of other tissues in tumors of the teratomatous type, especially in the kidney, vagina, testis, etc., but pure rhabdomyomas are found, generally small and capsulated, yet still in areas where mixed tumors

are common; apart from this, however, they exist in areas where striated muscle is normally present, such as the heart, the extremities, the nates, the orbit, etc.

In all these cases the fibres are of embryonic, imperfectly differentiated nature, sometimes showing only longitudinal striation, or transverse striation of only a part of the cell, and other characters, all of which point to the likelihood that they arise from cell rests

In some of these tumors the cells are comparatively undifferentiated, and these are naturally difficult to distinguish from sarcomas; in fact, malignant rhabdomyoma has been reported, in which the metastases showed striated muscle elements; in both these last forms there is considerable likelihood that the tumors arise from **sarcoblasts**, although they may have originated from cells of a yet earlier type.

The Neuroblastomas. — The elements of nervous tissue can give rise to tumors of two orders: lepidic originating from the ependyma or lining membrane of the spinal canal and the ventricles and hylic from the other nerve elements. That only is a true neuroblastoma which contains actual nerve cells or neurocytes. The so-called "**amputation neuroma**" is merely formed of regenerated axis-cylinder processes intermingled with inflammatory fibrous tissue: it is in no sense an independent growth. The true neuroma, or **neurocytoma** is one of the rarest of tumors. It must, however, be remembered that there are other cells of neuroblastic origin, namely, the neuroglia cells, giving origin to the **glioma**, the cells of the sheath of Schwann, giving origin to the **neurinoma** and lastly the ependymal cells, giving origin to the **ependymoma** (lepidic). Only such tumors as contain nerve cells should be classed as **neuromas**; further, if there be nerve fibres in a tumor which are in connection with a nerve cell outside the tumor, these are not independent, and so far as they are concerned, the tumor is not a neuroma. Although the true neuroma or ganglioneuroma is one of the rarest of tumors, yet it must be remembered that other constituents of the nervous system originate from the same order of cells as do the neurones.

FIG. 159

Still more "embryonic" neurocytoma from a child, aged sixteen months. (Drs. Tileston and Wolbach.) The ball-like arrangement of the cells with central fibrils is characteristic of an early stage in the development of a sympathetic ganglion. (Professor J. H. Wright.)

True Neuromas or Neurocytomas.—Tumors of large size have been found arising, in the abdomen, for example, from the solar plexus and the medulla of the adrenal, and also in connection with the brain, which contain cells of the type of sympathetic ganglion cells, with axones and dendrites. Found early in life, they are evidently developmental anomalies, arising from segregation of part of the neuroblast. Such have never been found of post-natal origin.

Another type of neuroma is formed of aggregations of round or pear-shaped cells, at first glance not unlike an alveolar sarcoma, running from which can be distinguished by special stains fine fibrils (axones); despite this fact such have been found to give metastases, and therefore are practically neurosarcomas.

Fig. 160
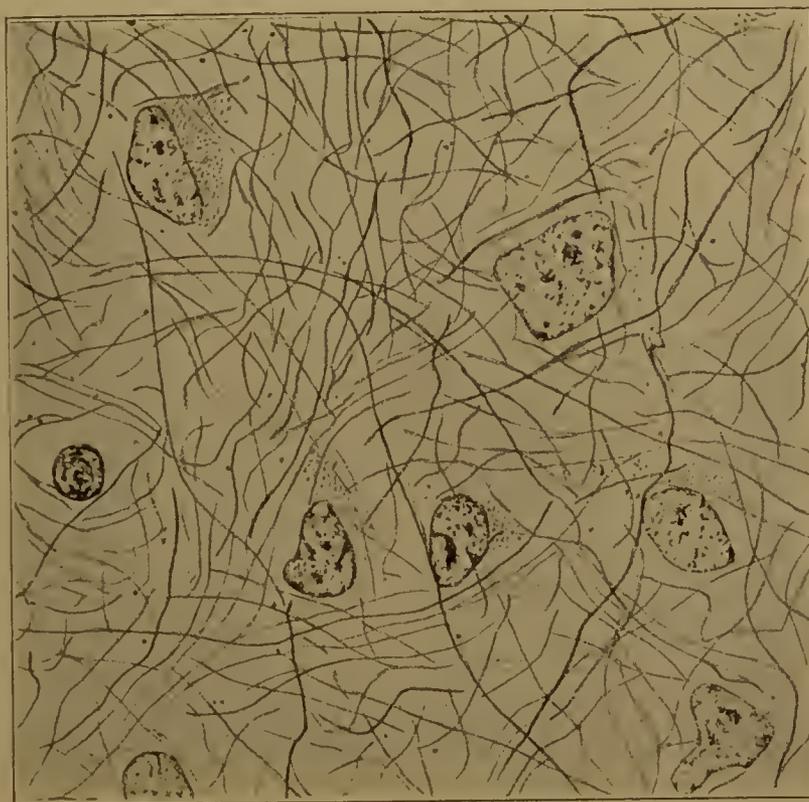
Glioma; numerous neuroglia fibrils surround the cells and run in all directions.   (Mallory.)

Glioma.—The glia cells are small, round, or oval, with a single nucleus and a small amount of protoplasm, having radiating fine processes running from one to another in all directions. These processes, like those in ordinary white connective tissue, are probably true processes of the cells that later may become separated and independent as fibrils. Tumors formed of these glial cells are found (a) in the brain, (b) along certain cerebral nerves, (c) in connection with the retina, and (d) over the coccyx, from the remains of the neural canal. In syringomyelia is found glial overgrowth that is to be regarded rather as a hyperblastosis (gliosis) than as glioma. Gliomas are hard or soft; the former, as found in the ventricular walls, are well defined; the latter

are diffuse, infiltrating growths, not capsulated, very vascular, and liable to be the seat of hemorrhages. To the naked eye they are areas of greater translucency than the surrounding brain tissue, with a bluish tinge, and pulpy by reason of the glairy fluid in the matrix. These last are found in the cerebral hemispheres and the corpus callosum, and may be of large size, replacing and compressing the brain tissue. Neither hard nor soft forms give rise to metastases; and recent studies go far to prove that many are strictly forms of hyperblastosis rather than gliomas arising from a single focus.

Retinal gliomas show more definite signs of malignancy, both in their capacity to infiltrate and to give rise to metastases. They are small, soft, gray masses projecting from the retina into the vitreous, may invade the sclera and extend into the orbit; or filling the bulb, the tumor may erode the cornea and project externally as a fungating mass. Histologically, they are formed of small cells, without processes,

Fig. 161

Fig. 162

Section of retinal glioma, showing relationship of cells to vessels and formation of "rosettes." (Ribbert.)

"Pseudo-epithelium," or secondary epithelium without basement membrane lining a cyst in a glioma, formed by modification of the superficial layer of glioma cells. (Saxer.)

arranged peculiarly around the vessels; glial fibrils may or may not be present. The perivascular arrangement suggests a perithelioma in appearance. In addition to this grouping of the cells, there are "rosette"-like groups around an apparent lumen (recalling an adenoma); but between the cells and the lumen is a clear layer from which minute conical projections into the space suggest the retinal cones. These retinal gliomas are formed of cells little differentiated, and are, we hold, properly gliosarcomas. The "rosettes" suggest a tendency toward lepidic arrangement.

In attempting to determine the etiology of gliomas, we are helped

by the fact that in the newborn there are occasionally to be found microscopic areas formed of glia with included nerve cells. Since they are found in the white as well as the gray matter, they seem to be misplaced inclusions or overproductions of nerve tissue, evidently developmental. This, and the liability of the young to the tumor, indicates that some, at least, of the gliomas originate from rests, even if many are of the type of diffuse hyperblastosis.

Ependymoma.—There are cysts, found in the gray matter, or in gliomas, lined by a true, often ciliated, epithelium (to be distinguished from those described upon p. 310 and shown in Fig. 162), which are evidently fœtal inclusions caused by the branching of the neural canal or by the cutting off of neuroblast which in its new site goes on to form epithelium of the nature of that which lines the neural canal. That neurones and glial cells develop alike from neuroblast explains why the ependymoma is never pure, because the neuroblast so separated gives rise to not only the ependymal cells, but to the glial and neurone cells as well, so that the ependymal cyst appears as an inclusion in a tumor of gliomatous nature. In this it resembles the minute cysts or rosettes seen in the retinal glioma.

Neurinoma and Neurinomatosis.—There is a very remarkable kind of tumor which appears as multiple nodules upon the stems of peripheral nerves, associated with subcutaneous nodules, which may reach several hundred in number, from the size of a pinhead to an orange or larger. These conditions we have already discussed when considering the condition of hyperblastosis. This condition has been variously known as **molluscum fibrosum, fibromatosis, von Recklinghausen's disease,** and many other terms.

The general appearance of the individual tumors is that of a true fibroma, moderately firm, but on microscopic examination, it is seen that interspersed among the fibroid tissue are individual nerve fibres, and this relationship has necessarily caused a great deal of debate. Regarding the tumors as brought about by overgrowth of the perineurium, they have been considered fibromas and wrongly termed neurofibromas. Others have recognized that the fibroid tissue is due to a proliferation of the cells of the sheath of Schwann, and believing these cells to be mesoblastic, have again held to the fibromatous theory. It has, however, been fully established by Kohn and Veroçay that these cells are of neuroblastic origin, that the growths are formed from a neurogenous tissue, and are derived either from the sheath of Schwann or from precursors of the same. These tumors, therefore, are to be described as *neurinomas*[1] or, more accurately, as neurinomatoid, because characteristically the tumors are multiple, they occur without sharp delimitation, and along the course of the peripheral nerves. There may indeed, in some cases, be a coincident increase in the true connective-tissue elements just as occurs in a uterine fibroid: there may also be

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[1] νευρον, a nerve; ἱς, ἱνος, a sinew or fibre.

exhibited, as in most of these cases of blastomatoid, a tendency for one or more of the tumors to manifest malignant sarcomatous characters. Along with this condition, there is often coincident existence of gliomatous areas in the brain and spinal cord, a condition of general vegetative activity in the nervous tissue. Just as neuroblast gives origin to neurones, glia cells, and these fibre cells, so in such tumors may be found the simplest form of neurocyte—small cells like lymphocytes—and various gradations up to cells of the imperfect neurone type.

Fig. 163
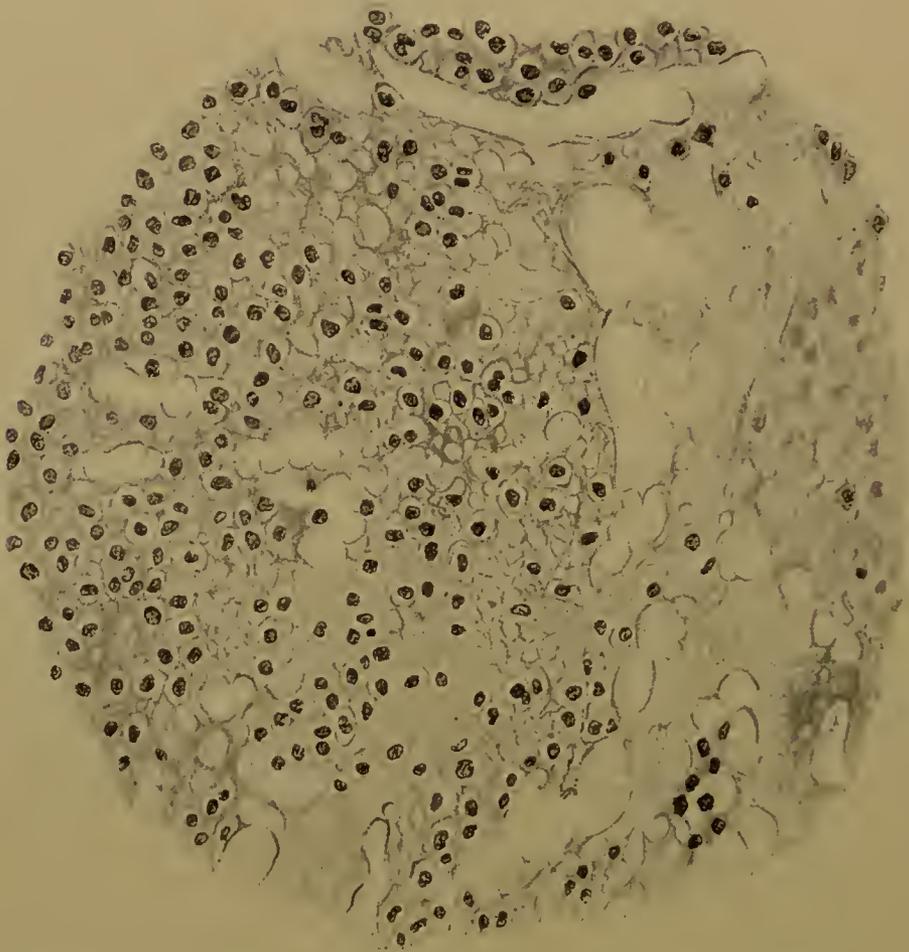
Section of a chordoma. To the right the cells are of the benign type, not unlike in arrangement to those of cartilage; to the left through active multiplication the cells are taking on a more sarcomatous type and the growth is becoming malignant. (Fischer.)

Chordoma.—This is a tumor of little or no importance which represents an overgrowth from the remains of the notochord, and so is of hypoblastic or entodermal origin. Occasionally small collections of large vesicular cells, separated by a homogeneous interstitial substance, are found in the intervertebral disks; most commonly an abnormal growth of these cells occurs just behind the pituitary body, the site of the upper end of the notochord, at the spheno-occipital synchondrosis, in the bone, through which and the dura mater it may project as a small mass of the size of half a pea, often intimately attached to the basilar artery.

ATYPICAL HYLIC TUMORS

Sarcomas.—While it is logical to discuss the atypical tumors with the typical tumors of each tissue, it would be cumbersome, by reason of the multiplicity of the sarcomas; they are, therefore, here dealt with as a class, the members of which have certain characters. The term has primarily a histological significance of which these characters are the basis.

The sarcomas are richly cellular tumors of the connective-tissue type, the cells being vegetative, imperfectly differentiated, resembling the embryonic mesenchyme, and developing a characteristic interstitial substance—the "hylic" arrangement. This arrangement can apply not only to tumors derived from the mesoblast (whether mesenchymatous or mesothelial), but also to certain tumors of epiblastic and hypoblastic origin; that is, *some atypical epiblastic tumors must also be regarded as sarcomas, and actively growing tumors of transitional lepidic characters are also to be considered as sarcomas.*[1] Such tumors are infiltrative and malignant, but the malignancy depends upon more than the mere form of cell present, for two tumors of equally small round cells may differ greatly in malignancy; the tissue of origin is of the greatest importance, and it may be said that the more nearly the cell approaches the cell of embryonic mesenchyme, the greater is the presumption of malignancy, but more important yet is this: that of two such tumors, the one that has departed the farther from its adult type of cell to reach this state, the one that has "reverted" the more, is the more malignant.

The sarcomas are not capsulated, but grow peripherally and invade the surrounding tissues by growth along tissue spaces. This leads to progressive destruction of the preëxisting tissue, and absorption of all that tissue save a supporting framework around the vessels and capillaries. Thus, the tumor cells are frequently arranged in masses separated by well-marked strands of connective tissue. *The sarcoma cells grow in the immediate neighborhood of the capillaries,* and the vessels

[1] This view of what constitutes a sarcoma is strongly combated by certain writers. They hold that the term should be restricted sharply to atypical tumors derived from the connective tissues proper, namely, white fibrous connective tissue, bone, and cartilage. We fail to see the force of this contention when all hylic tissues, if they have undergone sufficient anaplasia afford small round-celled growths of like histological arrangement. Certain gliomas, for example, exhibit areas of small round cells which from the rest of the tumor we know to be of glial origin—but here all glial fibres are absent. If in the brain we encounter a tumor formed wholly of this undifferentiated type of cell, how are we to know whether it originates from glial or connective-tissue cells? Histologically and clinically it comports itself as a small round-celled sarcoma. The idea of a gliosarcoma shocks these writers; we fail to see any logical reason why it should. Some would go so far as to do away with the use of the term altogether. Doing this they would restrict and cut down the nomenclature by one-third, speaking, *e. g.*, only of a typical and an atypical glioma. To us it seems distinctly useful to have the three grades: glioma (typical), gliosarcoma (intermediate), sarcoma of glial origin (most atypical).

are composed of a single endothelial layer beneath which are the tumor cells; the capillaries are wide and the tumor abundantly vascular. It is probable, but not certain, that there is a new formation of capillaries,

FIG. 164

Primary malignant lymphoma of stomach: *a*, predominating larger cells of lymphoblastic type; *b*, smaller lymphocytes. (High power.)

FIG. 165
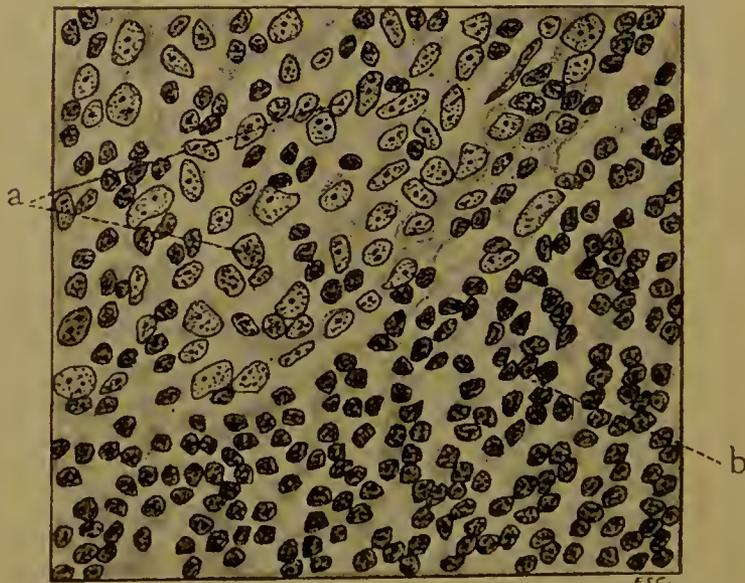
Portion of centre of active lymph node to show relationship of proliferating "mother cells," or lymphoblasts, to the lymphocytes to which they give origin: *a*, lymphoblasts of large size; *b*, lymphocytes. (High magnification.)

and that the sarcoma cells grow along these, just as the fibroblasts appear to extend outward among the growing loops of granulation tissue. In some sarcomas there are channels that have no endothe-

lium, so that the blood seems to make its way directly between the tumor cells. It will thus be seen that hemorrhage into the tumors is apt to occur, and that sarcoma cells are liable to become free in the blood stream, so that *metastases along the blood stream are characteristic of these growths*, and the lung is apt to be a common site of secondary sarcoma. Of course, metastasis can occur also along the lymphatics, so that involvement of lymph nodes is not diagnostic of carcinoma. Some observers consider that sarcomas possess no lymph vessels proper, but only occasional spaces and channels. Tumors growing as rapidly as do the sarcomas necessarily present abundant mitoses; cell inclusions, signs of degeneration, the so-called "sarcoma parasites" occur, but are not so frequent as the corresponding occurrence in carcinoma, and a frequent incident is the wholesale necrosis of a part of the tumor.

Forms of Sarcoma.—Although lack of cell differentiation is to a large extent accompanied by retention or acquirement of increased vegetative activity, yet the stages of undifferentiation or anaplasia are not entirely identical. A cell in its neoplasia can never reproduce a stage through which it has not passed in its normal development. Thus, a glia cell never passes through a spindle-celled stage in its development, and consequently, vegetative glia cells never produce a spindle-celled sarcoma; again, the lymphocyte is a smaller cell than the lymphoblast which produces it (Fig. 165), and a lymphosarcoma formed of vegetative lymphoid cells may be of a larger cell type than the adult lymphocyte (Fig. 164); it, also, may not be of the spindle-celled type. Only those cells which in the course of their (normal) development pass through a spindle-celled stage can give origin to a spindle-celled sarcoma; such cells are the connective-tissue cell and the plain muscle fibre. The statement has been made without sufficient justification that a typical, fully differentiated tissue or a typical blastoma cannot give origin to sarcoma tissue pure and simple; to say that this process cannot occur is equivalent to stating that fully differentiated cell arises from fully differentiated cell; but this, of course, is not the case. Either there are undifferentiated mother cells normally present from which the differentiated cell arises, or as in muscle and other tissues, the differentiated cell loses its specific features and becomes vegetative, in which state it is ready to proliferate. In a highly differentiated tissue, or in a typical blastoma, cells may lose their specific properties and become simpler; they need not revert all the way; regenerating muscle fibre reverts to the sarcoblast, or again it may revert all the way and resemble the primitive mesoblast. It follows, therefore, that a tumor may show any stage from the very lowest vegetative form up to the not quite perfectly differentiated cell. Being unable to function normally the tumor cell actually never does acquire perfection in differentiation.

The vegetative types of cell are simple and alike, from the small round cell to the larger round cell, to the oval cell, to the spindle cell; thus there are to be distinguished several forms of sarcoma: (1) small

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round celled, (2) round celled, (3) large round celled, (4) oat-shape celled, (5) small spindle celled, (6) large spindle celled, and (7) mixed celled, which last we employ when we are not able to say that one form of cell is the predominant type. These are **pure** sarcomas, but there are also the **intermediate** sarcomas in which the cells have not

FIG. 166
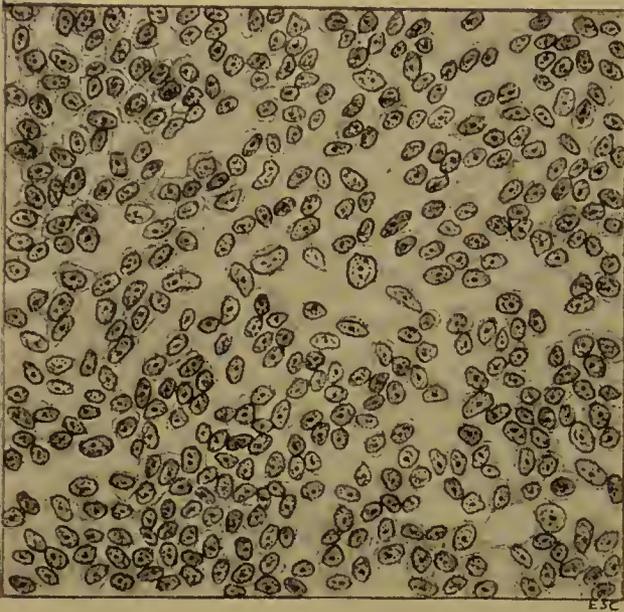
FIG. 167

Small round-celled sarcoma from skin. (High magnification.) (From Professor Klotz.)

Round-celled sarcoma infiltrating the heart-wall. (High magnification).

FIG. 168

Small round-celled sarcoma, infiltrating liver, advancing along a portal sheath: *V. P*, portal vein; *B. D*, bile duct; *A. H*, hepatic artery; *L*, liver cells.

become absolutely undifferentiated, so that certain tissue characteristics are preserved here and there in the tumor. As examples of this form might be mentioned fibrosarcoma, osteosarcoma, and chondrosarcoma. These more differentiated cells necessarily indicate a lesser degree of malignancy, and, on the other hand, the more vegetative the type,

the greater the malignancy; since the stages through which cells pass in becoming undifferentiated differ according to the cell concerned, it may, therefore, happen that cells which look alike may have become so through much or little undifferentiation, and thus, to repeat, the malignancy of superficially similar cells may be very different.

FIG. 169

Small Round-celled Sarcoma.— The most malignant and infiltrative growths to be found belong to this class. The cells are closely packed, stain deeply, and possess round nuclei with little cytoplasm; the interstitial reticulum is at a minimum. These growths are vascular and readily undergo hemorrhage; metastases occur by the blood stream and the lymphatics.

Large round-celled sarcoma.   (Ribbert.)

These cells are considered to arise from connective tissue, the growths, in fact, being not unlike a cellular granulation tissue; it may be recalled that the simple vegetative neuroblast cells, as seen in a retinal sarcoma, were of this sort, and it may well be that this is the least differentiated and the most actively vegetative of all cells.

FIG. 170
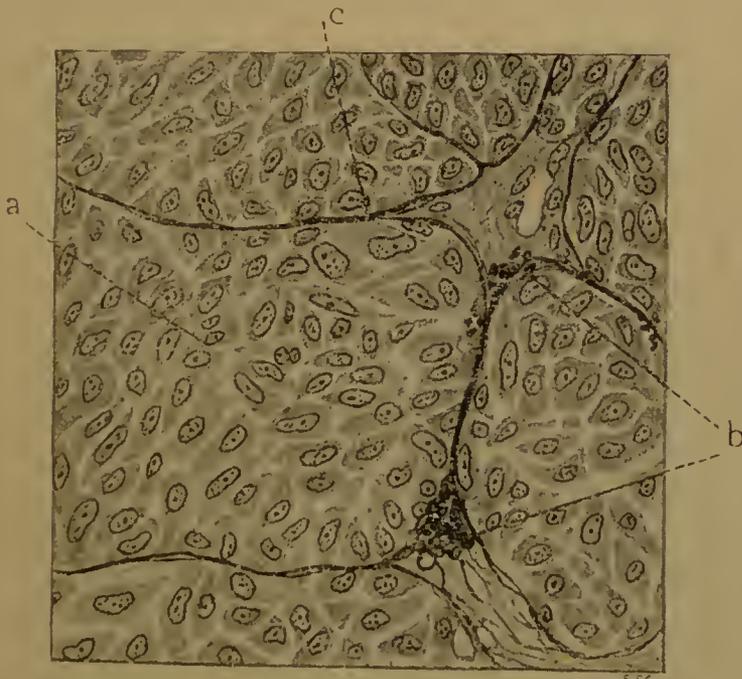
Alveolar blunt spindle-celled sarcoma (secondary, non-pigmented growth of melanotic sarcoma— or chromatophoroma—of skin): *a*, cell with two nuclei, recently divided; *b*, pigment containing leukocytes in stroma; *c*, septum between alveoli. (High power.)

The ordinary round-celled sarcoma, specified neither as large nor small, is merely an arbitrary group whose cells are of any size midway between this and the following.

Large Round-celled Sarcoma.—Although evidently related to the two forms already mentioned, the large round-celled sarcoma is quite a different tumor. The cells are fairly large with abundant cytoplasm, not

FIG. 171
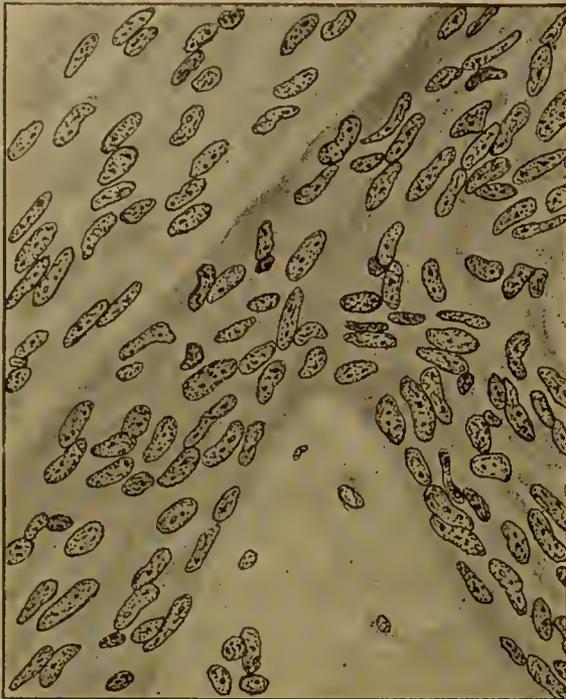
FIG. 172

Oat-shape celled sarcoma of unknown origin. (High power.) (McGill collection.)
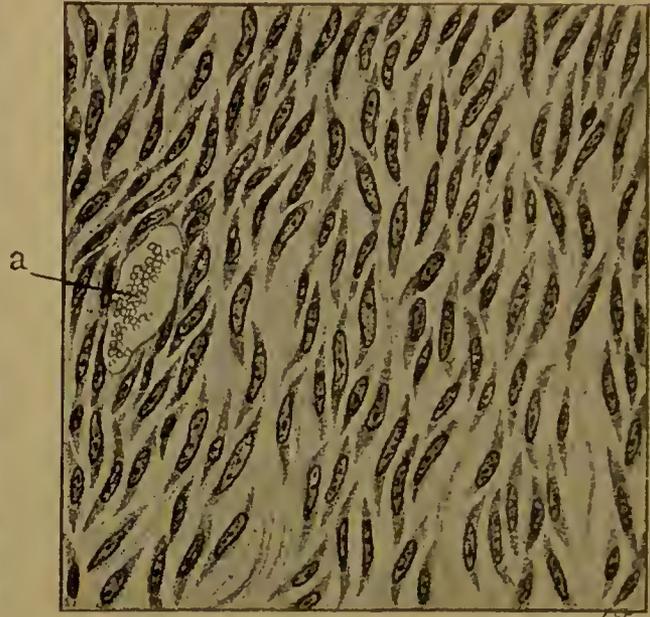
Spindle-celled sarcoma (recurrent, from forearm): *a*, delicate-walled blood vessel in tumor. (From Professor Klotz.)

necessarily round but sometimes oval and even polygonal. There is a fairly marked reticulum, and there may be in parts of the growth a definite connective-tissue stroma. They do not destroy and cause absorption of other tissues as readily as do the last-named forms. Such tumors are often found in connection with striated muscle; the most active, vegetative form of lymphoma presents also this kind of cell.

FIG. 173
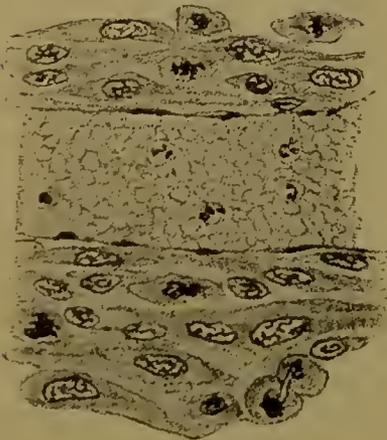
Large spindle-celled sarcoma. (Ribbert.)

The Oat-shape Celled Sarcoma.—It is perhaps overcare which seeks to differentiate this sarcoma from the spindle-celled sarcoma, but in contradistinction to the latter members of this group have long oval nuclei lying in blunt cells. We are not prepared to state that they originate from any special form of tissue.

The Small Spindle-celled Sarcoma.—The cells of this form are relatively small spindles, 15 to 20μ long, with oval or spindle nuclei, the cells appearing in bundles around the capillaries just as occurs in true fibromas. The relationship of these to connective tissue is so marked that their source

is evident; in fact, the fibrils which occur in connective tissue may be found in these tumors, which, compared with round-celled sarcomas, are far less malignant.

Large Spindle-celled Sarcoma (Fig. 173).—The nuclei are large and clearer than in the last case, are often vesicular and the cells vary greatly in their size and shape. Some arise from the periosteum, recalling the large spindle cells which occur in the giant-celled osteoblastoma; this is to be expected considering that both originate from the same tissue.

It will appear that there are not very sharply cut distinctions between the different groups of cells that have just been dealt with; this is due to the fact that undifferentiation has gone on to a different stage of completeness in each case, just as the growing cells attain different degrees of differentiation in their formative processes.

Intermediate Types of Sarcoma.—**Fibrosarcoma.**—It becomes largely an individual matter with the observer as to when a given tumor will be called fibroma and when it will be called fibrosarcoma; the fibroma itself shows far more numerous cells than does ordinary fibroid tissue. It is often difficult to say when the cells become so numerous in a given area as to justify the expectation that a tumor will become infiltrative and metastatic.

Myxosarcoma.—This name is given to tumors in which the myxomatous cells with their characteristic processes are a feature, but in which also there are islands of closely packed round cells without processes, which are evidently less differentiated and more rapidly growing.

Liposarcoma.—An obvious lipoma growing slowly for a long time may take on rapid growth and show sarcomatous areas where the fat cells are replaced by a tissue that is richly cellular. Such a tumor may, of course, give sarcomatous metastases.

Chondrosarcoma.—In a rapidly growing chondroma there is sometimes found a rapid transition from unmistakable cartilage to richly cellular tissue that is evidently sarcomatous; this is a gradual transition from highly differentiated cells to those less differentiated, the reverse of what occurs in the normal growth of cartilage. As the vascular sarcoma tissue becomes formed it can be seen to advance into and replace the more typical cartilage, so that we have the picture of cartilage formation and, superimposed upon the neoplastic cartilage, a sarcomatous modification.

Osteoid Sarcoma, Osteochondrosarcoma, and Osteosarcoma.—These three terms indicate different types of sarcoma exhibiting varying grades of the process of ossification.

The **osteoid sarcoma** is malignant, grows rapidly, and forms metastases; in it are areas intermediate between cartilage and bone, that is, there is a homogeneous matrix in which the cells are more like bone corpuscles than cartilage cells; sometimes there are several in one space. These cells are seen to surround thickly the osteoid lamella or mass; they are polymorphous, and sometimes giant cells occur; in

studying such a tumor one is convinced that the osteoid tissue is part of the tumor, and that the tumor cells have laid down the imperfect bone.

The **osteochondrosarcoma** is more perfectly differentiated, and there may be a deposit of calcareous salts in the lamellæ, while yet other cases show both true cartilage and true bone.

The **osteosarcoma** proper shows lamellæ and masses that consist chemically of true bone. Histologically it is imperfect, the bone being in isolated spicules or in thin, spongy irregular masses. Or, again, especially where the periosteum is concerned, radiating osteophytes appear. This is true bone, although in a tumor, just as there may be true muscle cells in a myoma.

There are some authorities who are unwilling to admit that true bone can thus exist as a part of a tumor, but the fact is actually so. Of course, the more perfectly and considerably this bony substance is laid down, the less malignant is the tumor, and we actually find in this series of growths widely different powers of malignancy, just as we find widely different histological pictures. The sarcoma elements may be spindle cells, polygonal cells of various sizes, giant cells (especially in central growths), and over the growth there is generally a periosteal formation of bone which is thin and readily broken, giving rise to the familiar "egg-shell crackling." As a rule, they do not form metastases until the superficial periosteum is broken through.

Rhabdomyosarcoma.—This form appears in the kidney and elsewhere, especially as part of the multipotential tumors that have been mentioned. They may show imperfect muscle fibres, transversely striated, spindle cells with longitudinal fibrillation, or large polymorphous, often multinucleate cells of sarcoblastic type, although it is not necessarily safe to say that all such tumors arise from sarcoblastic cells only.

Gliosarcoma.—We have referred to these tumors in connection with the retina, and it will be recalled that the determination of such, as distinct from a simple round-celled sarcoma, often depends upon the retention of a few imperfect glial fibrils and cells.

PRIMARY LINING MEMBRANE OR LEPIDIC TUMORS (LEPIDOMAS)

It must be understood at the outset that while these tumors show a combination of tissues yet the essential part of them is the epithelial or glandular, that is, the lining-membrane element. It is essential to have a stroma, and the very presence of the lining-membrane elements renders the stroma more proliferative, but this growth is not necessarily more than irritative, that is, it is not truly blastomatous.

TYPICAL LEPIDIC GROWTHS

Papilloma.—The term papilloma conveys to the mind nothing but an anatomical description of the form of the tumor, and makes no statement about its histological nature, yet for the class of tumors so

described there is no term which is more used by the clinician, and we have therefore to utilize this term, coupled with a qualifying adjective to indicate the nature of the papilloma under discussion. Papillomas are outgrowths from surfaces covered by epithelium, whether squamous or columnar, having a connective-tissue core to each individual process.

Of Irritative Origin (incorrectly called Papillomas).—There are certain growths of irritative origin which fulfil in a sense the foregoing definition:

(a) **Warts.**—These are outgrowths of the corium covered by a thick hypertrophied epiderm; they arise apparently from irritation, are

Fig. 174
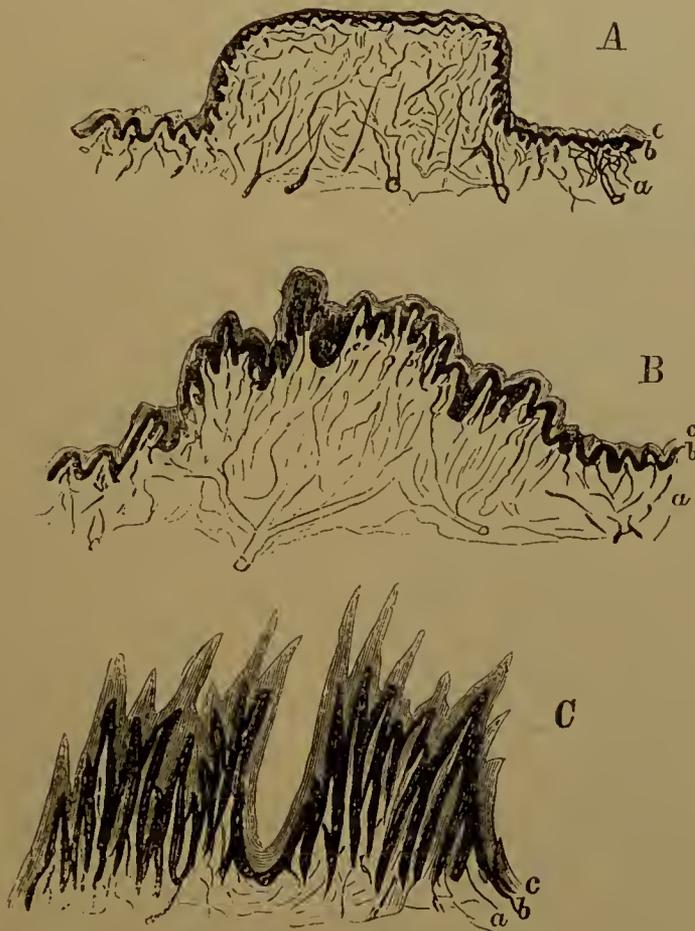
Various grades of warts and cutaneous papillomas. (Perls.)

common in childhood and youth, and tend to disappear. Some consider them infective, and there is considerable evidence in favor of their being transmissible (Fig. 174).

(b) **Molluscum Contagiosum.**—This is a definitely contagious skin disease arising as small red masses, becoming warty, undergoing central necrosis, and discharging cheesy matter. The epiderm is not greatly overgrown, and there is as yet no definite evidence as to a parasitic origin; some interest attaches to the condition because in it have been described intracellular bodies, like the so-called cancer bodies, which at present are counted to be of degenerative origin.

(*c*) **The Condyloma.**—Condylomas are warty, nodular, or cauliflower-like growths, occurring as a multiple development on the external genitalia, in the anal region, or in the mouth. They occur as a sequel to uncleanliness in the presence of venereal infection. It is probably safe to say that syphilitic infection is always present, although the condyloma must not be confounded with the so-called simple **venereal wart.** The condyloma shows an outer wall of thickened overgrown epithelium lying upon hypertrophied connective tissue, which is the seat of inflammatory infiltration; essentially benign in itself, the condyloma may become the seat of a true blastomatous growth.

Fig. 175

Condylomata of the vulva.   (Orth.)

(*d*) **Cutaneous Horns** (*Hyperkeratosis*).—These are strange-looking processes of horny constitution which project oftenest from the scalp and the face; they are movable, the base being soft. The horn is an overdevelopment of the keratinous material in the skin, along with a failure of the same to be rubbed off, so that an accumulation occurs. More than this, however, the cells throughout the entire epidermis may become

Fig. 176

Section of portion of the wall of a coccidial cyst in the liver of a rabbit: *a*, fibrous capsule; *b*, proliferated epithelium of bile duct, with papillomatous outgrowths; *c*, coccidia free in lumen.

keratinized, while the vascular core of the papilla or horn is preserved; it seems, therefore, as if we had to do with a degeneration

rather than a true blastoma, or even a purely irritative phenomenon. (See later under Degeneration.)

(*e*) **Coccidiosis.**—To indicate how papillomatous growths may arise from irritation we may note the occurrence of papillomas due to the coccidium, which is one of the sporozoa. This parasite appears to be almost devoid of marked irritative power, and yet, as a result of its very slight irritation, there is excessive proliferation of cells, especially of the epithlieal type, with scarcely any tendency to necrosis. Its stimulus, therefore, appears to be little stronger than a physiological one. In the liver of the rabbit cysts are found, and in these cysts the epithelium of what was originally a bile duct becomes papillomatous, and projects in dendrifying masses; at first glance such a condition appears to be truly new growth, but the continuance and the further growth of the papillate masses occur only with the continued presence of the coccidia, and metastasis never occurs.

(*f*) **Bilharziasis.**—Even more blastomatous in character than the last is this condition, in which (Fig. 178) growths in the rectum and the bladder are initiated by the ova of Bilharzia

FIG. 178

Bilharziasis of the rectum, to show papillomatous overgrowth of the mucosa: *H*, cavities filled with blood. (Looss.)
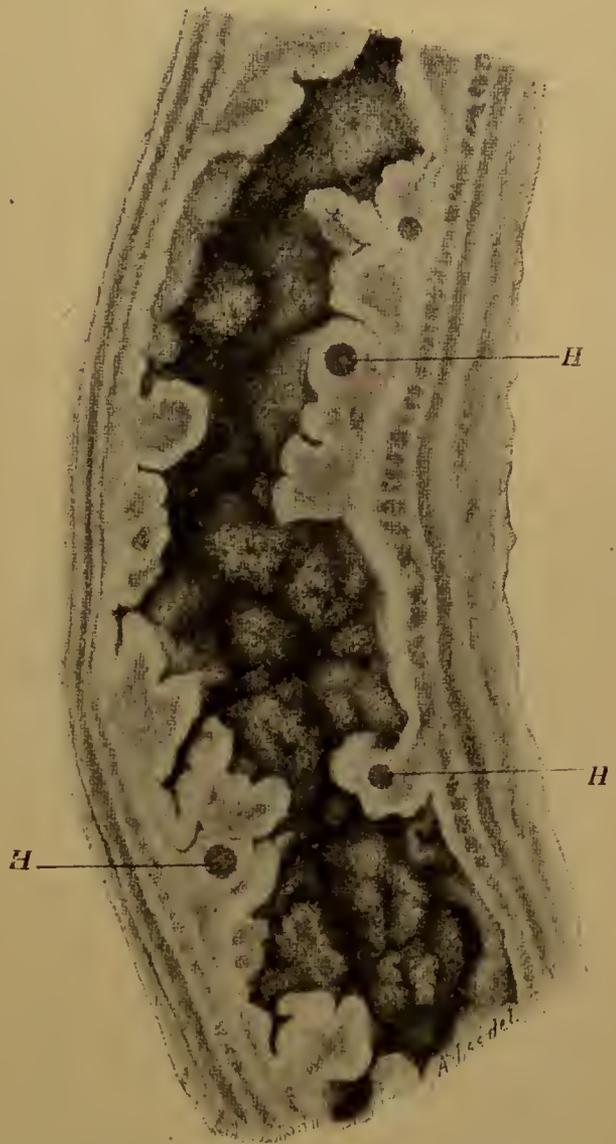
FIG. 177
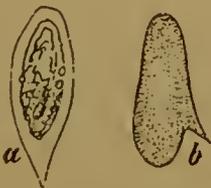
Ova of Bilharzia (Schistosoma) hematobium, to show *a*, terminal, *b*, lateral spike. (Perls.)

hematobium. The eggs of this parasite having a spike, are able to travel through the tissues and in the bladder and rectum induce hematuria and melena. In both these organs we find papillomatous proliferation of the mucosa and not infrequently this irritative overgrowth gives place to definite carcinoma. It is evident that the stimulus to growth and the habit of growth are acquired by the epithelium during the long-continued presence of the parasite, and that the final assump-

tion of carcinomatous process is the expression of this habit of growth, and is not dependent upon the continued presence of the egg.

Blastomatous Papillomas.—(a) **Soft Papillomas.**—Of these growths there are many forms, from a mere nodular protuberance of the mucous membrane to a mass of delicate long finger-like processes; the nodular process, and each of the finger-like growths alike, has a framework or stock of connective tissue, in which run the vessels, while on the outside the covering is of the epithelium of the part, often with abundant mitoses and often, too, showing the utmost specialization, as when, in the intestine, it shows abundant goblet cells; on the other hand, it may be modified by its position (Figs. 179 and 180) so that a growth in the bladder may be covered by round-celled epithelium like that normally found in the deep layers of the vesical lining.

FIG. 179   FIG. 180
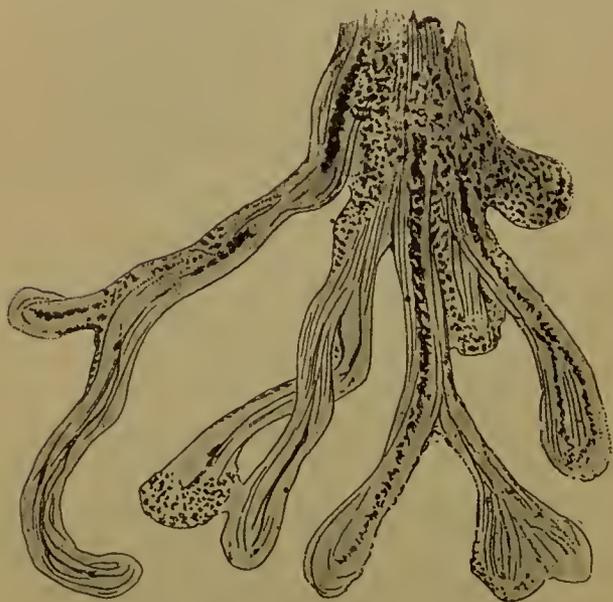
Papilloma of bladder to show the long, finger-like papillomatous outgrowths. (Ribbert.)
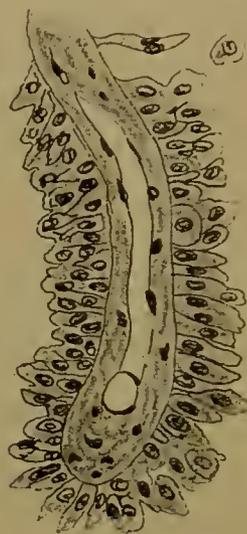
One of the fine processes of a papilloma of the bladder more highly magnified to show the central fibrous core or stock with vessels.

(b) **Intracystic Papillomas.**—These are similar papillary growths, forming an infolding and reduplication of the inner lining of a cyst or of the acinus of an already-developed adenoma, the branching processes tending to fill up the cavity of the cyst. Each of these processes has the customary core of connective tissue, and this core of connective tissue and vessels is secondary to the epithelial overgrowth; this, in fact, is to be considered as the mode of origin of all papillomas, the epithelial activity appearing to stimulate the increase of the supportive tissue. Sometimes papillomas (as happens not infrequently in the bladder and alimentary canal) give place to malignant growth, the cell growing inward instead of outward, infiltrating the underlying tissues.

Adenoma.—An adenoma is a new growth of glandular epithelium, typical in that the copy reproduces closely the original, or, expressed differently, having its epithelium arranged similar to the arrangement of the epithelium in the organ from which it grows; if that tissue be com-

posed of glandular acini with definite lumina the adenoma is in the form of acini with lumina; if, as in the liver, the epithelial cells form in solid masses, then the adenoma is of solid masses without lumina; if developing from the epithelium of a duct, then the adenoma takes on the character of a duct. There is thus a well-marked variation among the adenomas, and before being able to state how typical or atypical a tumor is, it is necessary to know from what tissue it originally sprang. A knowledge of histology must supply this information.

The power of growth being relatively slight, that of function is not entirely in abeyance, and the secretory cells in an adenoma are apt to

Fig. 181
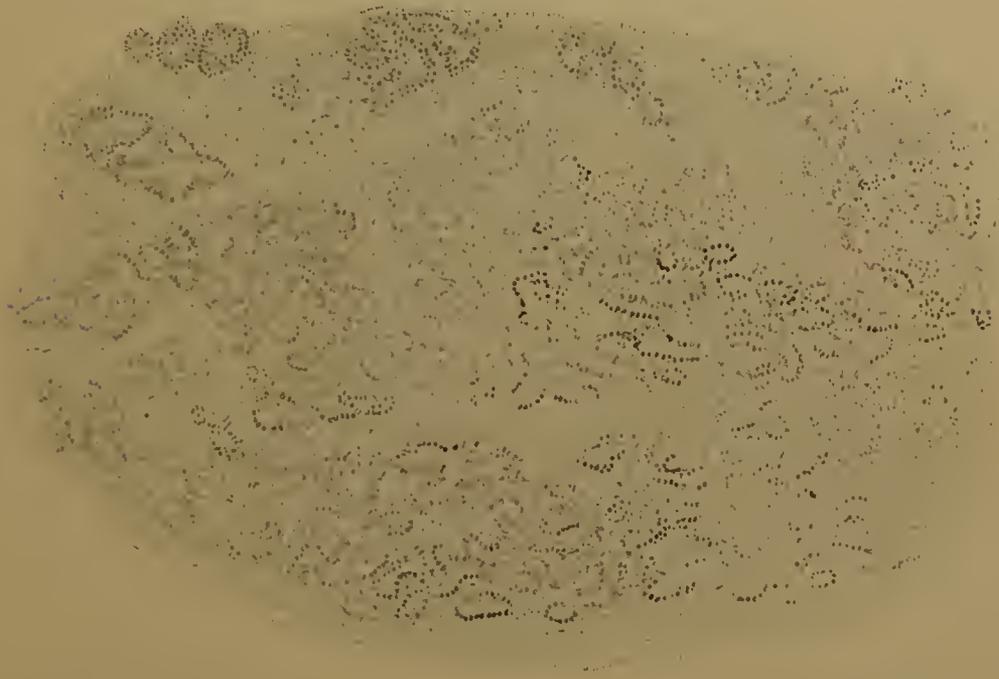
Adenoma of bile ducts, formed of acini resembling those of normal bile ducts. (Wätzold.)

retain some power of secretion. Adenomas of the intestine may exhibit goblet cells and discharge mucus; of the thyroid, some form colloid, and of the liver some produce bile; and as such growths are sometimes encapsulated within the tissues, and are incapable of discharging their secretion, the secretion is apt to accumulate, distend the structure or the tubule, and form cysts, the **cyst-adenomas.**

In studying such a growth as the adenoma we come at once to the difficulty presented by such a fact as this, that two tumors of the same organ may develop histologically similarly, and yet one will form at the most a benign cystic growth, and the other a solid tumor mass, having some of the characteristics of the carcinoma. We have, in fact, to recognize that in the adenoma we have a grade of overgrowth, different only in degree and not in kind from the inflammatory or irritative hyperplasia of epithelium on the one hand, and a malignant glandular carcinoma, on the other. As we have done before, we can

divide the overgrowths of glandular tissue into (1) irritative and congenital glandular hyperplasia, (2) adenoma (encapsulated), and (3) adenomatosis (non-encapsulated).

We have said that two adenomas may grow from the same organ, one being cystic, the other not; one being capsulated outside of the mother-tissue, another being capsulated within the tissue; one may have ducts that open and allow secretion to be discharged, while the other is closed up and may become cystic. Because some of these adenomas, like normal glands, connect with the ducts of the organ, it becomes very difficult to separate them from inflammatory hypertrophies of the organ. For example, a diffuse fibroid induration of the mammary gland may histologically exactly resemble a section taken from the middle of an encapsulated adenoma; and the same is true of the liver, where by the process of regeneration, new masses of liver cells spring up, which exactly resemble the adenoma of the liver arising without definite cause.

These similarities arise from the fact that irritative and regenerative hyperplasia, adenoma, and carcinoma are three stages which can be shown in succession by the same tissue, the differences being differences of degree and not of kind.

The cell-rest theory fails to explain satisfactorily the occurrence of the adenoma; it is more rational to think that if cells (in cell-rests) which have never attained full differentiation, may under simple stimuli take on independent and blastomatous characters, the same can be done by fully differentiated tissues. In inflammation we see these cells reverting quickly to the vegetative stage, and an atypical arrangement. Why may not the same cause that sets up independent growth in cell-rests set up independent growths in cells produced from differentiated tissues?

Histologically, the stroma is an important part of the adenoma. Typical adenomas show basement membrane between the cell layer and the stroma; when growth is rapid and atypical, that is, when the growth is carcinomatous, the basement membrane may be absent. While the gland cells and the stroma are dependent, one upon the other, the former is the more important; in fact, the growth of the stroma follows that of the epithelium, and in transplantation of adenocarcinomas in mice it is the transplanted gland cells that form the tumors, the stroma being furnished by the new host. The growth of stroma secondary to the growth of epithelium is a phenomenon of chemiotactic nature, and this secondary overgrowth is to be regarded as a reaction on the part of the body for its protection against the invader, the overgrowing epithelium. This reaction on the part of the body is a factor in the arrest of new growths, the arrest occurring in two ways. If, on the one hand, a given cell entering a tissue induces no reaction, its proliferation becomes arrested because it has no vessels and no stroma; if, on the other hand, there is excessive reaction, then the connective-tissue overgrowth may cut off the nutrition of the developing neoplasm. This merely bears out what we have previously

noted, namely, that the development of a blastoma depends upon the resultant of two factors, the proliferative capacity of the growth, and the reactive property of the organism. We shall here deal one by one with the different degrees of overgrowth.

1. **Congenital Glandular Hypertrophy.**—An example of this is the massive growth of the mammary gland which may follow upon the ordinary development .of puberty; such glandular overgrowths have been known to secrete milk, and to prove, histologically, to be an excess of normal mammary gland.

2. **Irritative Hyperplasia.**—This is evidenced by increase in size of the gland, due mainly to fibrosis, as occurs frequently in the breast. Glandular overgrowth, though to a moderate extent, does apparently here exist. A similar condition is the overgrowth of the mucous membrane of the digestive tract at the edge of an ulcer; prostatic hypertrophy probably belongs to the same category.

3. **Adenomatosis.**—This is the condition, closely related to the last mentioned, in which portions of a gland or a surface become the seat of adenoma, the overgrowth occurring, not from a single focus, but simultaneously from many foci at the same time. Examples of this form are the multiple polypoid adenomas of the alimentary tract, or multiple adenomas of the liver.

4. **Adenoma Proper.**—These are the demarcated, encapsulated, benign overgrowths of glands. They are not numerous compared with the examples of adenomatosis, and they appear to originate from cell-rests. When the cell-rest is formed of gland tissue normally communicating with the exterior, complete encapsulation results in cystic formation, and the cyst may become the seat of intracystic papillomatous growth. An absence of secretion indicates either origin from non-secreting cells, or a highly marked grade of anaplasia. Here also belong the encapsulated cystic adenomas of the mammary gland, as well as the large group of adenomas which arise from the remains of the Wolffian duct, and the cyst-adenomas of the ovary.

THE ATYPICAL LEPIDIC GROWTHS—CARCINOMA

Up to the middle of the nineteenth century, any malignant growth was designated a cancer. With the development of morbid histology, pathologists came to use the term cancer as synonymous with carcinoma and as sharply contrasted with sarcoma. Within the last few years, with the development of "cancer research," and with workers in this department studying both carcinomas and sarcomas, we are reverting to the older use of the term. We shall thus employ the term cancer indiscriminately to indicate a malignant growth of any order, the term carcinoma to denote only cancers of epithelial and glandular origin.

Carcinoma.—We here consider atypical growths of both covering epithelium and of gland tissue, and point out that the properties of

both are alike, to such an extent that the most atypical forms are scarcely distinguishable. Here if anywhere are found exceptions to the rule that the greater the degree of anaplasia, of departure from the adult normal histological type, the greater is the malignancy, for some of these carcinomas in the primary growth depart but little and are exceedingly malignant, while some that are greatly anaplastic are of relatively mild malignancy. A good example of the latter is **rodent ulcer** (called **basal-celled carcinoma**), a very anaplastic kind of growth which for months or years shows a local malignancy, but which in many cases fails to form metastases. Of those apparently slightly anaplastic, yet very malignant, as exemplified by some adenocarcinomas, careful examination will show slight departures from the normal, such as the absence of a basement membrane, and some slight tendency to infil-

FIG. 182
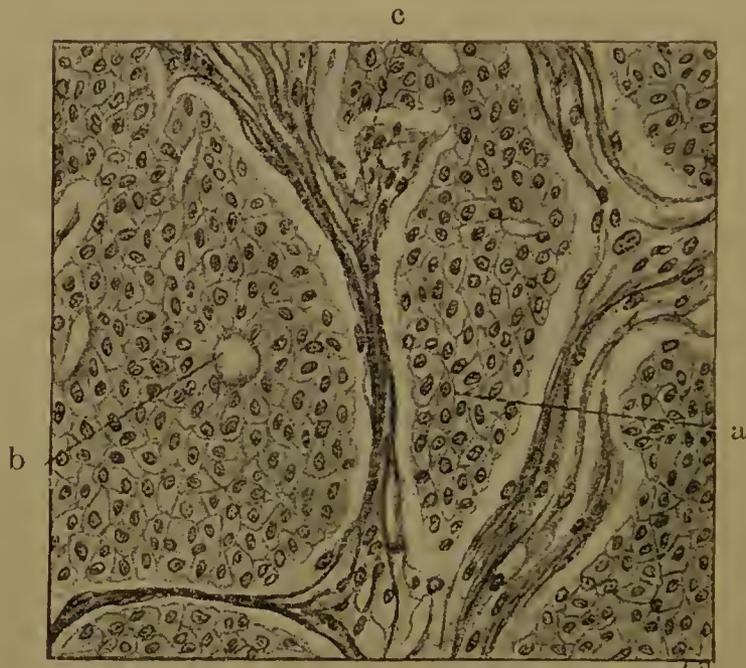
Carcinoma of breast (preparation of Dr. Rhea), stained by Mallory's connective-tissue stain, to show relationship of gland-cell masses to stroma: *a*, mass of infiltrating, anaplastic, or aberrant gland cells; *b*, lumen (or pseudolumen) developed within a mass of cells, showing persistent tendency to retain the normal relationships; *c*, the connective-tissue stroma.

tration. *We thus regard as carcinomatous all cases in which there is infiltrative, and apparently independent growth of epithelial or gland cells into the surrounding tissues, and this whether of slightly atypical or markedly atypical cells.*

Relations of Tumor Cells and Stroma.—As in the adenomas, the primary tumor element is the epithelial cell; it makes its way into the tissues and in so doing sets up a reaction on the part of the tissue so invaded. Such reaction is often very well marked at the growing edge of squamous-celled carcinomas, where it may be evidenced by a distinctly inflammatory appearance, with a small-celled infiltration (Fig. 183). Many of these cells are leukocytes, and actually penetrate the growing tumor cells, especially if these latter are degenerated; they are often taken up

and appear as inclusions in the tumor cells. By the poor staining reaction shown by the leukocytes in the region of a rapidly growing carcinoma, they are evidently themselves undergoing disorganization. There are indications that the actively growing carcinoma cells feed upon the preëxisting tissues, and apparently by phagocytosis, by extracellular ferments, and by preparatory solution, the tumor cells replace the tissue cells and use them as foodstuffs. But, on the other hand, the stroma of the tissue is used to form the stroma of the tumor, and the presence of the tumor may stimulate such stroma to proliferate; this proliferation may be merely of connective tissue, or may be of a higher order of tissue, as is seen in the production of new bone in a secondary carcinoma situated in a bone; or yet further, the stroma may be excited to an atypical overgrowth itself, giving rise to what is a true **carcinoma sarcomatodes.**

FIG. 183
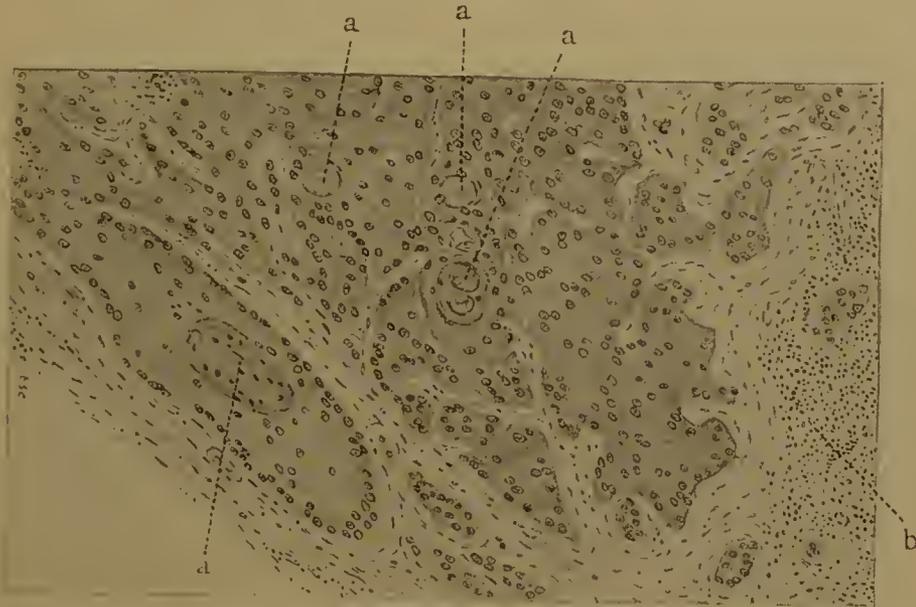
Epithelioma of lip: *a, a*, epithelial "pearls;" *b*, small-celled infiltration of surrounding tissue at periphery of new growth.

According to the degree of reaction we are accustomed to use certain descriptive words to denote carcinomas of different consistence: (1) **medullary,** where the cell growth is abundant, and the stroma inconsiderable, the resulting tumor being cellular, soft, and like marrow (medulla); (2) **scirrhous,** in which the stroma is abundant, the tumor cells being scanty and compressed; and (3) **carcinoma simplex,** where no marked predominance of one over the other is noticeable. (Plate IX.)

At the edge of a carcinoma the cells generally stain deeply and are intensely vegetative, and while less so centrally, there may yet in this position be mitotic figures, indicating that the growth is not only peripheral. Generally, degeneration progresses fairly rapidly in the deeper parts, and this degeneration sometimes varies according to the function of the tissue from which the tumor is derived; thus fatty changes are common in mammary gland tumors (recalling the active part taken by the cells of that gland in supplying absorbed fats to the milk),

and mucoid changes in tumors of the alimentary canal (in evident relationship to the normal function of the goblet cells of the mucous membrane).

"**Cancer Bodies.**"—These are bodies, found in and between carcinomatous cells, which have often been supposed to be parasites, and the cause of tumor growth, but which are at present considered to be cellular degenerations. Thus we encounter small, hyaline, spherical bodies of varying size, the mean size being that of a red corpuscle, which stain intensely red with fuchsin, and lie singly or in little groups attached to one another, both intracellular and free in the stroma. They are known as "**Russel's bodies,**" after their discoverer, are met with not only in malignant growths, but also in inflammatory areas, and are considered to be examples of hyaline degeneration, but whether of red corpuscles, of cells, or of albuminous matter is still unsettled. Other intracellular bodies are of various forms. There may be a single, round, homogeneous mass

Fig. 184

Fig. 185

Intracellular bodies of the type of Russel's fuchsin bodies from a case of cancerous leukoplakia, in cells of the plasmacell type. (Krompecher.)
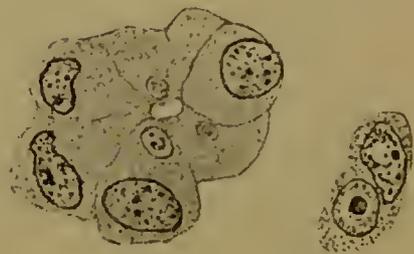
Cell inclusions in cancer cells—the supposed parasites. It will be seen that the bodies are to the inner side of the cell toward the lumen; in the position, that is, of modified secretory products. (Greenough.)

pushing the nucleus aside; or such a body with a metachromatic central part, or surrounded by a clear space or a peripheral ring staining differently from the rest of the body, or a peripheral ring with processes connecting it with the cytoplasm; or, again, a central body may be surrounded by a ring of smaller globules; or through the cytoplasm may be scattered abundant small bodies lying in apparent vacuoles; or even large, amœboid, gregarine-like forms are seen, sometimes in the cell and sometimes outside it. With so many forms, and such failure to correlate results on the part of many observers, one may be forgiven for some scepticism as to these bodies being causative. Although the descriptions recall the successive stages of a protozoan, with progressive enlargement and final setting free of spores, yet the study of the microchemical reactions of mucin, hyaline, amyloid, keratin, and other degeneration products shows that the same reactions are obtained in the case of these bodies. It is, of course, possible that some one or more of these bodies may eventually prove to be protozoan, but in the present state of our knowledge, there is no sufficient ground for supposing that in them we have discovered the cause of malignant growths.

Site of Origin.—It is often impossible to determine the first site of a malignant growth, because by the time of operation or death it has become too extensive; but in the case of superficial growths it can often be determined that the origin is from a single point; yet even this does not mean that the tumor is necessarily the progeny of a single cell. By serial sections it has been possible to see that although in a single section the alveoli of tumor cells appear separate, yet in different planes they are all connected in a series, or a set of series, for it may be possible to determine that there are more centres than one of origin, that the growth is pluricentric, arising from several cells in the same region simultaneously.

Fig. 186

Early epithelioma of tongue, to show (a) region of origin by down-growth from preëxisting epithelium; b, b, epithelial pearls; c, small-celled infiltration in surrounding tissue. (Petersen.)

Occasionally several primary growths, widely separated, are encountered, as occurs in the multiple superficial growths of chimney-sweeps or of workers in paraffin, and best of all, in the frequency with which both ovaries are affected by carcinoma. Fairly frequently, too, an individual may exhibit two or more distinct forms of primary growth in different parts of the body, although both of these may not be malignant, as for example where uterine fibromas or thyroid adenomas coexist with carcinomatous growth elsewhere. It is not possible to go farther than to state that the same instability of tissue that permits

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the overgrowth of tissue in one place in a typical (benign) way, affecting numerous tissues, allows atypical overgrowth in another, or even subsequently in the same place; that is, the multiple growths arise as a sequence of a vice of development or from the development of multiple cell rests. The development of now single now multiple tumors is paralleled by the state of affairs we find in infection. There, generally, we find a single focus of origin, although in some cases there appear to be multiple simultaneous developments; the single focus (remaining single) is explained upon the presumption that the resistance of the body is raised, and further invasion at other points is resisted. In a like way, when tumor growth originates, the body resistance is sufficient to prevent further development elsewhere, although not strong enough to overcome the tumor growth already instituted. That this resistance is real is shown by the fact that a mouse inoculated with carcinoma is immune to a second inoculation, but if the primary growth be removed this immunity is quickly lost.

FIG. 187
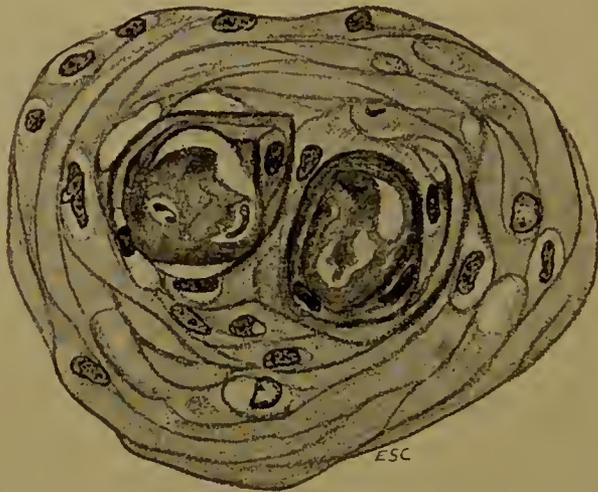
Epithelial pearl from section of epithelioma of tongue to show structure. (Immersion lens.)

Squamous-celled Carcinoma (Epithelioma).—Tumors of this order originate from squamous epithelium, and are, as such, chiefly of epiblastic origin; but since hypoblastic lining membrane may be of squamous type, as in the œsophagus, this also may give rise to squamous-celled carcinoma, and as the skin glands of epiblastic origin can give rise to gland carcinomas it is evident that no absolute distinction can be made in the way of considering one of epiblastic and the other of hypoblastic origin. According to its relationships and its functions, a given lining membrane develops squamous or columnar or cylindrical epithelium, and according to the type of the mother tissue is the malignant growth that arises from it.

The squamous-celled carcinoma presents solid columns of cells passing in various directions, and in sections cut now transversely, now longitudinally, now obliquely, lying in a relatively abundant, vascular stroma, which may show considerable "small-celled" infiltration (Fig. 186). In the typical column there is an outer layer of closely set

cells, staining deeply, which represents the Malpighian layer. Within this may be several layers of "prickle-cells," which, as the centre is approached, become less well stained, flattened, and finally keratinized. Thus the centre of the column comes to be formed of concentric, flat, keratinized cells, staining strongly with eosin, and constitutes on section the **epithelial pearl**. The formation of the pearl can be understood if we imagine that the skin, instead of growing down in a solid column, is invaginated as if pushed before an imaginary finger. The outermost cells of the projected part would be those of the Malpighian layer, and the innermost ones the normally keratinized cells of the surface. If the imaginary finger were now withdrawn, and the projection laterally compressed to obliterate the space left by the finger, the solid

FIG. 188
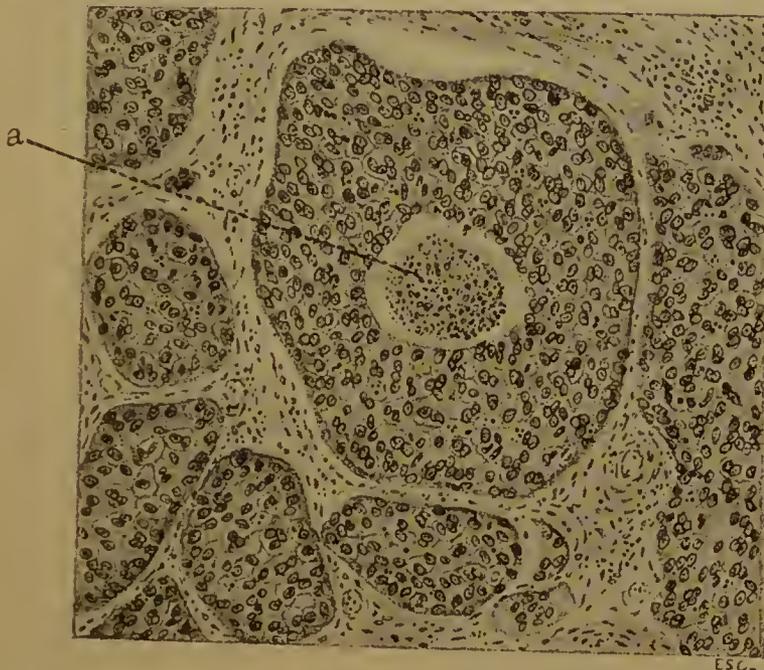
Impure or transitional epithelioma of antrum of Highmore ("basal-celled carcinoma"), in which instead of central keratinization and pearl formation, there is central necrosis and autolysis (*a*), with production of lumen-like space.

column so resulting would show precisely what is seen in a down-growing process of epithelium. In less typical growths, the differentiation between the cells of different layers is by no means so clear, and with greater degrees of anaplasia the cells may be round, polygonal, or even spindle-shaped, as may happen in rodent ulcer (Fig. 189), and in this connection it is to be remembered that the extreme anaplasia is not necessarily a sign of extreme malignancy. These tumors which show a failure of differentiation toward flattened and keratinized cells have been called the **basal-celled carcinomas** (Fig. 188), on the ground that such arise wholly from the basal cells of the Malpighian layer, although, as a matter of fact, as this is the actively growing part of the epithelium, all squamous-celled cancers rise from this layer; *it is the degree of ana-plasia*, the incapacity to develop beyond a certain point into the flattened

and keratinized cells that determines the existence of such tumors. There are certain differences to be seen in the squamous-celled carcinomas according to the site of their origin. Skin and tongue tumors

Fig. 189　　　　　　　　　　　　　　　Fig. 190

Portion of edge of a rodent ulcer.
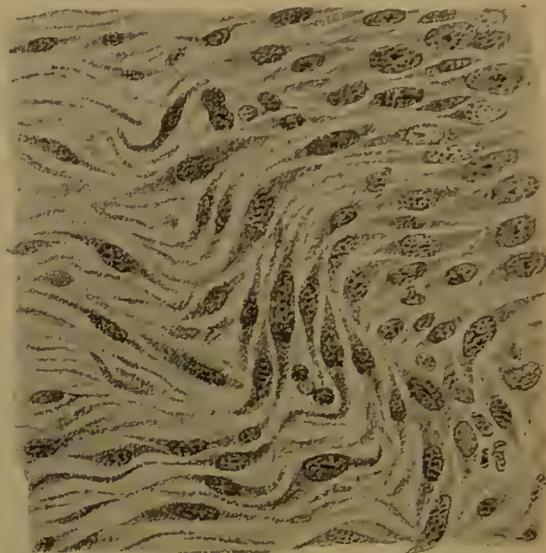
Part of the same at *a* more highly magnified, to show assumption by the epithelial cells of a spindle-shaped type.　(Krompecher.)

are apt to give well-marked pearls; œsophageal tumors are not so apt to show them, just as normally in the œsophagus the keratin development is not marked. The more rapid, too, the growth, the more atypical it is, and the less apt are the differentiations to appear, just as the process

Fig. 191
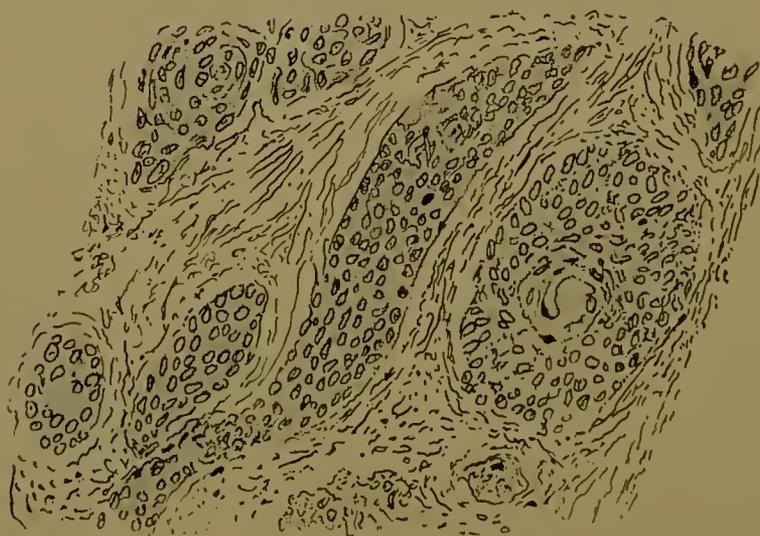
Aberrant squamous epithelioma of gall-bladder.　(von Hansemann.)

of keratinization on the skin requires the lapse of considerable time, and a constant slow progression of removal from the deeper, better-nourished layers below; where the growth is rapid and the cutting-off of the cells

PLATE X
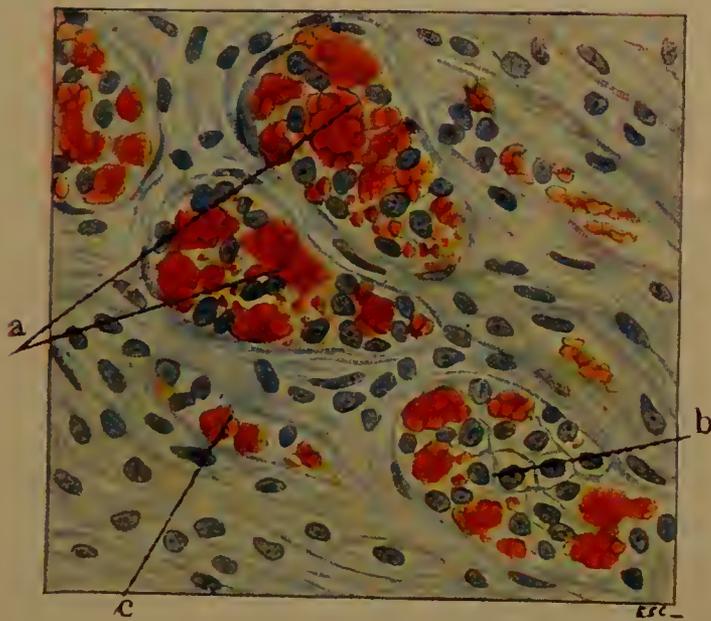
Alveoli from Edge of a Carcinoma of the Mammary Gland.

Stained by Sudan III and hematoxylin, to show the retention of fat-accumulating property on the part of cancer cells derived from the mammary gland (specimen of Professor Klotz). *a*, cells distended with small, fatty globules; *b*, another cell devoid of them; *c*, remains of shrunken cancer cells.

from their nutrition correspondingly hastened, more active degenerations (even necrosis) are liable to occur (Fig. 188).

Squamous-celled carcinomas are found occasionally in regions which normally possess columnar epithelium, such as the larynx, bronchus, stomach, uterus, and gall-bladder. It is in these very regions that we encounter, either as the result of metaplasia or otherwise, islands of imperfect squamous epithelium, and apparently it is from such cells that these tumors originate. They are not infrequently mixed, showing both epitheliomatous and glandular carcinomatous constituents.

Gland-Celled Carcinoma.—These tumors differ somewhat according to the structure of the mother-tissue; from tubular glands we are apt to obtain tumors that show, or attempt to show a tubular arrangement;

FIG. 192
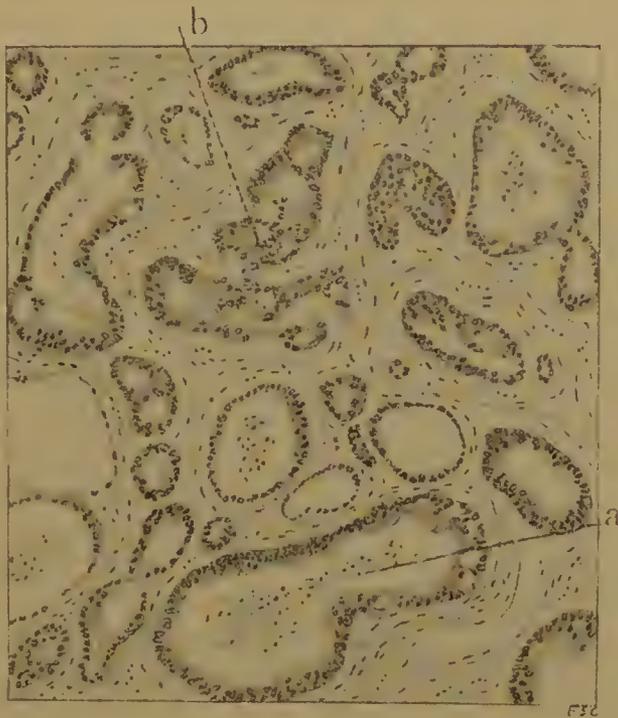
Adenocarcinoma of rectum (from preparation of Professor Klotz): *a*, section across tubular down-growth with large lumen; *b*, more solid mass of aberrant gland cells forming multiple lumina.

from acinous glands, tumors that have a grape-like arrangement; from the liver, a tumor of cells arranged in solid masses running in irregular strands. As before stated, it is necessary to consider the tissue from which it arose, before one can say how typical or atypical is a certain tumor. In the tumors which show a distinctly glandular form, there may be a relatively orderly arrangement, with an attempt to form lumina or, on the other hand, there may be no such attempt, so that we arrive at the forms in which the gland formation is lost and solid masses of cells occur with more or less abundant stroma, according to the amount of which, as already stated, we call the tumor medullary, scirrhous, or simple. To make any farther-reaching classification of the gland carcinomas is hardly necessary; at most it may be convenient for descriptive purposes to define a tumor by an adjective

FIG. 193

Medullary cancer.   (Ribbert.)

FIG. 194
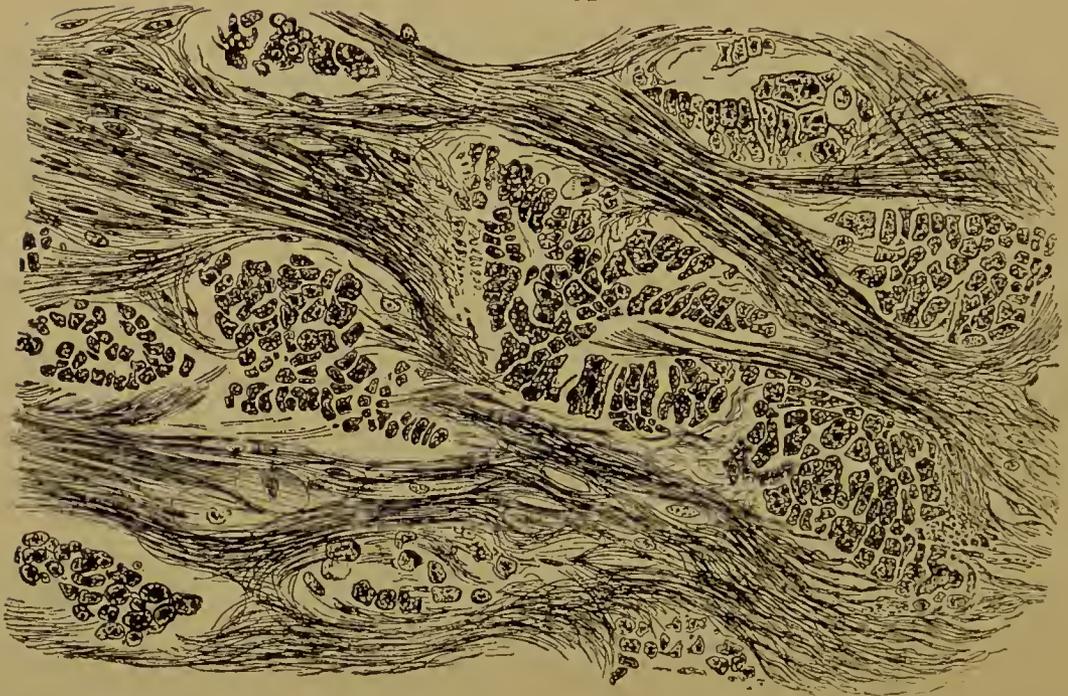
Scirrhus of breast.   The cells are compressed and degenerated and the stroma relatively abundant.
× 250.

FIG. 195

Carcinoma simplex.   (Ribbert.)

descriptive of the form of its cells, as columnar, cubical, etc.; the same carcinoma may, in different sections, show pictures so diverse that one is in danger of laying too much stress upon the characters that appear predominant in this or that section.

Degeneration.—The superficial carcinomas tend to ulcerate, by reason of the ill-control exercised upon the blood supply and the exposure to trauma or infection against which they are unable to protect themselves. Extensive mucoid change, **"colloid"** degeneration, occurs, especially in the carcinomas of the digestive tract; the tumor cells seem to retain the power of producing mucin, but are apparently unable to properly excrete it, so that it becomes heaped up in the cells, distend-

FIG. 196

Colloid cancer, showing large alveoli with cell remains, within which is contained the gelatinous colloid material. × 300. (Rindfleisch.)

ing and eventually killing them. Whole alveoli may suffer from this change, so that careful search is necessary to discover cells to give a clue to the nature of the tumor.

Of all tumors, carcinomas or malignant epithelial growths are the most important, both to the pathologist and the clinician. Judging from statistics they are rapidly increasing in their frequency, and when not recognized early are so hopelessly fatal, that it becomes of the highest importance to recognize them at the earliest possible moment and so permit of their removal before they have infiltrated too extensively.

MESOTHELIOMAS AND ENDOTHELIOMAS (TRANSITIONAL LEPIDOMAS)

It will be recalled that our classification grouped together all those lining membrane tissues of mesothelial and mesenchymatous origin, derived secondarily from the mesoblast. Of these there are four groups: (1) tumors arising from the development and vestiges of the Wolffian

and Müllerian ducts; (2) those arising from organs which, while they come into intimate relationship with these, nevertheless as regards their essential constituents, are of separate mesothelial or mesoblastic origin (ovaries, testes, kidneys; with this group may be included the adrenals); (3) other mesothelial tumors derived from the serous surfaces, and (4) the endothelial tumors.

1. **Urogenital Duct Tumors.**—Whether the urogenital ducts gain a secondary lining of hypoblast or epiblast or whether, because of their very early differentiation, the properties of their mucous linings are relatively stable and fixed, certain it is that the tumors derived from them are usually of a purely lepidic type—true adenomas and true carcinomas—with very little tendency to take on secondarily hylomatous (sarcomatous) development. Thus, in the uterus and prostate, for example, we get pure adenomatous and carcinomatous growths. Yet, though rarely, it does happen that a tumor of one of these areas may show most marked hylic characters (as in one of our cases of prostatic tumor where the primary growth was typical carcinoma, but the extension sarcoma-like, in the judgment of some well-known pathologists). Such tumors have clearly transitional properties.

2. **Tumors of the Ovary, Testis, Adrenal, and Kidney.**—In considering the tumors of the kidney, it is necessary to remember that the Wolffian duct provides the distal, collecting part of the tubule, and the mesenchyme the glomerular epithelium and that of the main part of the tubule. In the ovary and testis the primitive kidney, intimately connected with the Wolffian duct, is involved, along with the germinal mesothelium. Thus it comes that, while in these organs we meet pure adenomas showing no sign of reversion, we also find a series of transitional tumors which in places appear to be adenomatous and in other places sarcomatous, and yet other areas where one passes into the other, and the cells in the sarcomatous areas may even be spindle shaped. Such tumors, once for all, dispose of the idea of the strict bounds that were formerly supposed to exist between carcinomas and sarcomas, and that such tumors can exist is due to the common embryogeny of the primitive tissues.

Adrenal Tumors.—It has been said that there are in the ovary, testis, and kidney, tumors of fixed type, which fixity is perhaps due to the stability of the Wolffian epithelium. In the adrenal, however, there is no such doubtful origin, and yet we find in it transitional tumors.

The adrenal, it is true, arises from two sources: the medulla originates in connection with the sympathetic nervous system, the cortex from mesothelial elements. In the medulla originate tumors that are true neurocytomas, with rudimentary ganglion cells and non-medullated fibres, which evidently arise from cell rests of the sympathetic system; the cortical tumors, however, are entirely different.

First, there are accessory adrenals; they are composed of cortical tissue, lying in the adrenal capsule or in the adrenal itself or outside it, or even in the kidney and more rarely in the liver, while at times

they have been carried down in development and appear in the ovary or testis. When such are found to hypertrophy, we deal with an adenomatous phenomenon. These tumors show the typical cortical tissue,

Fig. 197

From the edge of a small nodule of new growth in the adrenal cortex, showing every transition from *a*, cells undistinguishable from the surrounding cells of the cortex to small cells with deeply staining nuclei of sarcomatous type. (Adami.)

Fig. 198

Similar conversion or modification of cortical cells of adrenal into tumor cells. (Woolley.)

Fig. 199
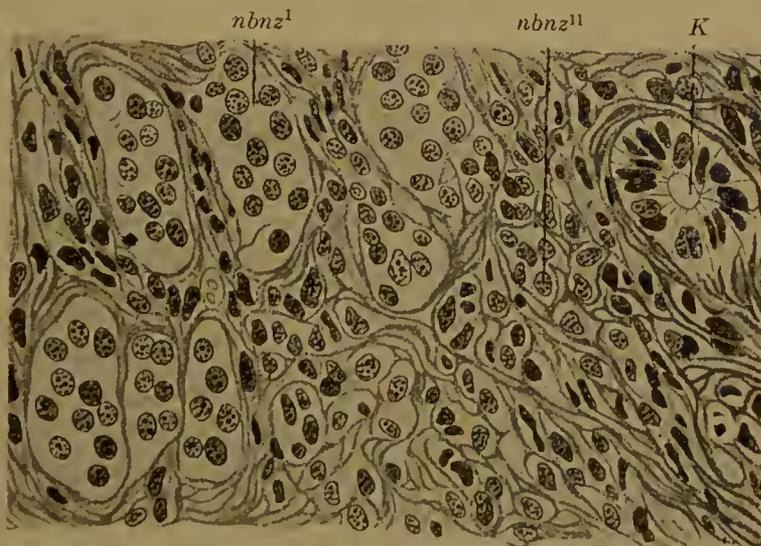
Hypernephroma of kidney. Transition from adenomatous to sarcomatous type of growth: $nbnz^1$, adenomatous overgrowth of solid columns or masses of cells of adrenal type; $nbnz^{11}$, transition to sarcomatous arrangement; K, a kidney tubule involved in the growth. (Debernardi.)

columns of cells lying in a meshwork of capillaries, the cells containing fat and myelin droplets. At times, instead of small growths, we find tumors of large size, in which we have the normal appearance of

columns of cells, the cells large, and crowded with fat and fat-like globules and glycogen, which last is constantly present in the growing adrenal. Such tumors, again, are evidently adenomatous. But there are other tumors which in parts may be like these, and in other parts show cells smaller, less fatty, more deeply stained, with transitions from adenoma to sarcoma, and definite sarcomatous tissue; these may show metastases that are clearly sarcomatous. All these, to use the modern expression, are **homotopic hypernephromas** (hypernephros, the adrenal). The name hypernephroma[1] is more commonly employed in connection with a remarkable tumor of the kidney, in the belief, first propounded by Grawitz, that tumors of this order found in the kidney, originate from adrenal cell rests, that they are **heterotopic hypernephromas**. It cannot be said that there is a complete consensus of opinion as to the nature of these renal growths. Possibly some of those which are found in the kidney cortex arise from the kidney instead of the adrenal, that is, are nephromas instead of hypernephromas. The two cortices, that is, of the kidney and the adrenal, are somewhat related embryologically so that tumors arising from them must possess closely related characters. This view is supported by the latest workers on the subject, namely, Wilson and Davis. When such a tumor of the kidney tends to form tubules instead of solid columns of cells, its renal origin is a reasonable supposition.

These tumors are apt to be vascular, the cells being in close contact with the capillaries or sinusoids, and they are prone to hemorrhage; metastases by the blood stream readily occur, and especially is the tumor apt to grow by continuity along the veins to the vena cava.

A useful term to describe all these transitional tumors of the adrenal, kidney, ovary, and testes is **mesothelioma.**

A mesothelioma is thus:

I. A tumor arising from tissues which, while of mesothelial origin, possess in the adult state lepidic characters.

II. When typical and of slow growth, it is an adenoma.

III. When atypical and of rapid growth, a sarcoma, although transitions between adenoma and sarcoma are to be seen.

IV. The secondaries are sarcomatous.

3. **Mesotheliomas of Serous Surfaces.**—These are flat, nodular tumors, spreading locally over the pleura, more rarely the peritoneum or pericardium, looking to the naked eye like a localized inflammatory thickening, and under the microscope, like a carcinoma. They evidently arise from the endothelium lining the serous cavity affected. A relatively abundant stroma is present, containing elongated acini, formed of irregular, swollen, often cubical cells. Here we deal with a carcinoma-like tumor that has originated from the part of the mesoblast that has taken up a lining-membrane function.

4. **Endothelioma.**—The endothelioma is a tumor arising from the lining cells of a vessel, and may be a **hemangio-endothelioma**, from a

[1] An indefensible term: we might as well speak of a tumor of the foot as a pedoma.

blood vessel, or a **lymphangio-endothelioma**, from a lymph vessel; in a tumor of long establishment it may be difficult to make the distinction. In discussing overgrowths of blood vessels, we have to consider first the typical ones, and this leads us to the consideration of some tumors that are not blastomas, along with some which are.

Angiomas.—Most so-called angiomas (tumors having vessels as their main constituent), whether hemangiomas or lymphangiomas, are not true blastomas; *they possess no power of independent growth.* Mere dilatation of spaces, even if preceded by aplasia and followed by atrophy of the surrounding tissues, is not growth; nor is the increase in length of a vessel (as in a cirsoid aneurysm), nor increase in the thickness of walls (as in cavernoma) to be considered as more than physiological. We find widening of preëxistent vessels, either congenital, due to a lack of coördination between the amount of tissue to be supplied and of vessels to supply it, or postnatal, due to obstruction (as in hemorrhoids) to compensate for which the capillaries undergo dilatation. But this is not blastomatous growth. Properly, most of what are called angiomas are **angiectases**, or dilatations of vessels produced, not by virtue of independent cell growth but by some physical force or other stimulus. Saying this we do not mean to infer that true angiomas do not exist: with them we shall deal later.

Blood Vascular Tumors ("Hemangiomas") which are not Blastomas. —1. **Obstructive Telangiectases.**—The best-known example of this is the **hemorrhoid.** The hemorrhoidal veins of the anal region communicate with the main and with the portal venous system; situated close to the surface and poorly supported externally, obstruction to the onward passage of blood leads to dilatation. Similar capillary and venous dilatation occurs in "nutmeg" liver, in the vessels of the nose and cheek, and in the frequently observed **varicose veins** of the legs.

2. **Aneurysm.**—This is the dilatation of an artery produced as a result of weakening of its wall. The only form of aneurysm which might at all be considered as angioma-like is the form known as **cirsoid**, which may show itself at birth and grow rapidly afterward, having a tortuous, worm-like appearance, and sometimes reappearing in the same region after removal. It is probably due to a combination of congenital weakness of the wall with inadequate discharge of blood from the vessel.

3. **Congenital Telangiectases.**

(*a*) *Telangiectatic Nævi.*—Some nævi (**pigmented moles**) are purely cutaneous outgrowths with melanin-containing cells; the majority contain, in addition, dilated capillaries or may indeed be areas of simple **telangiectasis** ("birthmarks"). The "blue nævus" is an extreme grade of the same condition, often very extensive. The association of telangiectasis with congenital pigmentary disturbance suggests that we are dealing with a vice of development; the simple birthmark is a capillary dilatation, and the same state may be found in bone, muscle, or even in the brain. The blue nævus has larger spaces,

where, by pressure atrophy, septa have been broken down, while the septa that yet exist and the containing capsule indicate overgrowth from pressure—stress hypertrophy.

(b) *Cavernoma.*—This form can scarcely be separated from the foregoing, and is a frequent abnormality of the liver, in which it is found most frequently of the size of a pea, although occasionally as large as an orange. It is supposed but not certainly known that some are congenital, while in

Fig. 201
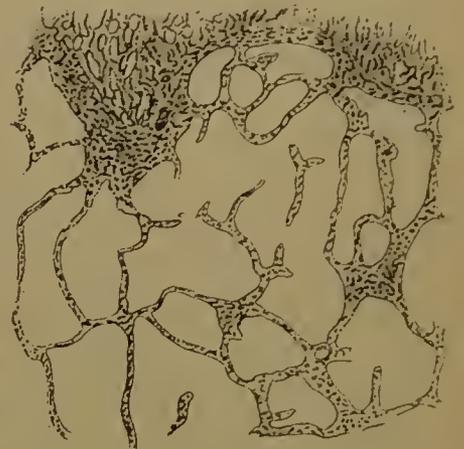
Section of small cavernoma of liver, showing the cavernous and communicating vascular spaces, from which the blood has been removed. (Ribbert.)

Fig. 200
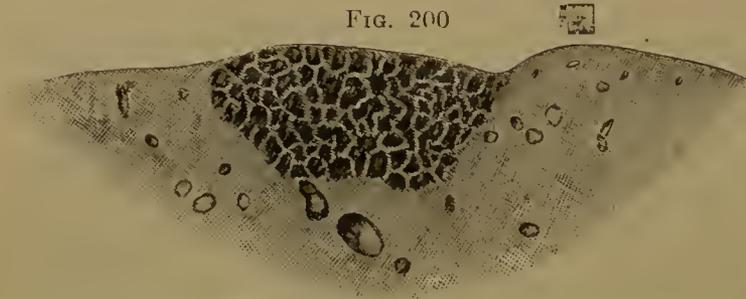
Cavernoma of liver. Gross appearance. (After Ribbert.)

others it may be that a localized atrophy of liver cells is followed by compensatory dilatation of the capillaries. Microscopically, a caver-

Fig. 202
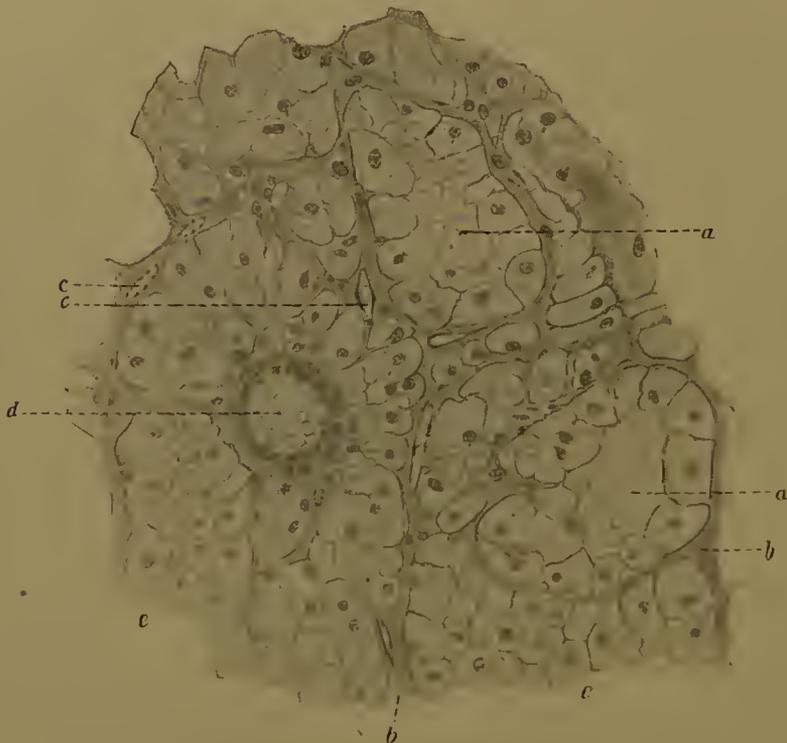
Section from a hemangio-endothelioma of bone: *a*, large vascular spaces filled with erythrocytes and surrounded by large, clear, cubical endothelial cells, which in parts, as at *c*, form solid masses; *b*, stroma; *d*, larger and *c*, smaller bloodvessels. (Driessen.)

noma consists of large irregular blood spaces, communicating one with another, lined by endothelium and having septa of a fibrous nature,

in which often are seen pigment particles. Thrombosis or calcification with formation of phleboliths occurs in them. Their congenital origin is ascribed to the failure of the original capillaries to become clothed with or to enter into connection with liver cells; and a strange observation has been made, namely, that they are not connected with surrounding capillaries, and, according to Ribbert, cannot be injected through the hepatic vein. Most often they show no sign of independent growth and are not blastomas.

True Typical Blastomatous Hemangiomas.—Angioma Simplex.—The true angioma shows an actual proliferation of capillaries with some ectasis, and the striking feature is the endothelium, which is large,

Fig. 203

Section from a case of hemangioma simplex, exhibiting progressive enlargement and extension. (Borrmann.)

rich in cytoplasm, and often more than one layer deep. These have been found in the skin, chorion, and muscle, and the tumor consists of a congeries of such proliferated endothelial tubules—sometimes called the benign angioma. Cases which show departure from the type even to the extent of showing columns of cells instead of tubules ought to be classed with the hemangio-endotheliomas—the atypical angiomas; much more so when they exhibit metastases. In the endothelial growth we see the one main factor which makes these blastomas.

Lymphangioma.—Here, as in the hemangiomas, the majority of tumors called lymphangiomas are really lymphangiectases. These

may be independent or may occur in connection with tumor growth, in which case the angiectasis is subordinate to the tumor growth; dilated lymph channels are often seen in connection with all forms of overgrowth. When independent and unassociated with neoplasms of other orders, lymphangiectasis may be inherited or acquired, and is one of three grades, between which occur all stages of transition.

FIG. 204

Section from a lymphangiectatic polyp of the nose, showing the greatly distended lymph channels lined by delicate endothelium and the œdematous interstitial tissue. (High power)

1. **Simple Lymphangiectasis ("lymphangioma simplex").**—These occur congenitally as slightly raised areas upon the skin breaking through easily, and when broken, "weeping" persistently (**lymphorrhœa**). They occur most frequently on the face and neck, and vary greatly in the depth they extend into the tissue. Anatomically like these, but acquired, are the dilatations of lymph channels secondary to obstruction that are found in **elephantiasis** (filarial).

2. **Cavernous Lymphangiectasis ("Lymphangioma cavernosum").**—These correspond to the cavernomas but contain lymph, not blood; mostly congenital, they include examples of **macroglossia** (enlargement of the tongue), **macrocheilia** (enlargement of the lip), and other forms of congenital elephantiasis, brought about by a defective ability of the tissues to discharge the lymph.

3. **Cystic Lymphangiectasis.**—The most striking examples of this are found in cases of "**cystic hygroma**," where multiple large, clear cysts occur below the ear, or submaxillary, or above the clavicle. The swelling is tense, and the large cysts often do not communicate with

one another; they are lined with endothelium and have strong, fibrous walls. This is not due merely to obstruction, but the secretory activity

Fig. 205
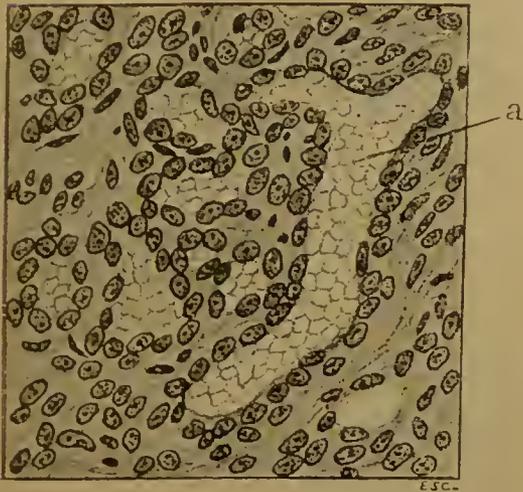
Fig. 206

Hemangio-endothelioma from nose of child, showing development of new capillaries (*a*). (Prof. Oskar Klotz.)
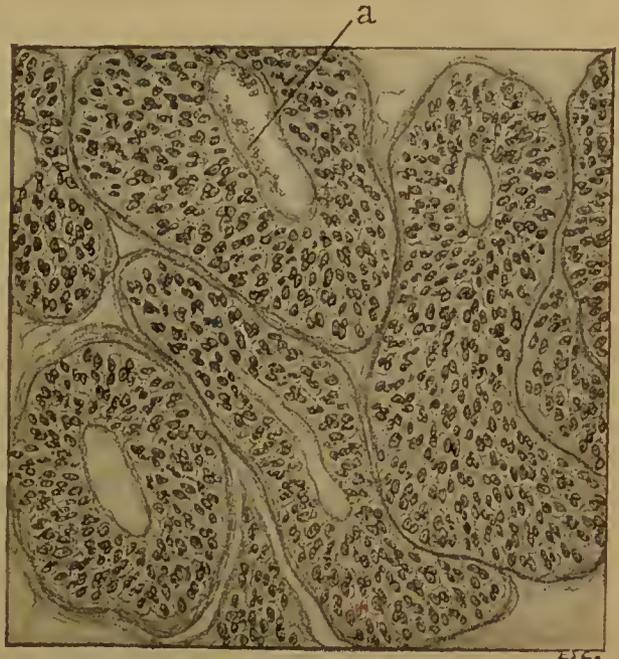
Section from a perithelioma or perithelial angio-sarcoma (from the collection of Dr. Rhea), showing the relationship of the central blood vessel *a* to the new growth.

Fig. 207

Lymphangio-endothelioma. The small cells are proliferated from the endothelial lining of lymph sinuses, and the larger multinucleate cells are giant-cell masses of like origin. The position of the cells relative to one another is in life preserved by a fine stroma. (Prof. Oskar Klotz.)

of the endothelium is likewise responsible. Not to be confounded with it is "**cervical hydrocele**," where a cyst, lined by epithelium, arises from

part of a cervical duct or fissure.   A true hygroma may appear in the sacral region, a form of the congenital sacral tumor.

Atypical Angiomas.—Hemangio-endothelioma.—The most characteristic example is that developing beneath the dura mater, where it forms nodules that displace brain substance or spread as sessile masses.   The appearance of the microscopic field is striking; the tissue consists of numerous whorls of concentrically disposed cells, which are flattened but not tightly packed, especially at the centre, where one may often distinguish the lumen of the bloodvessel.   If cut in a direction not
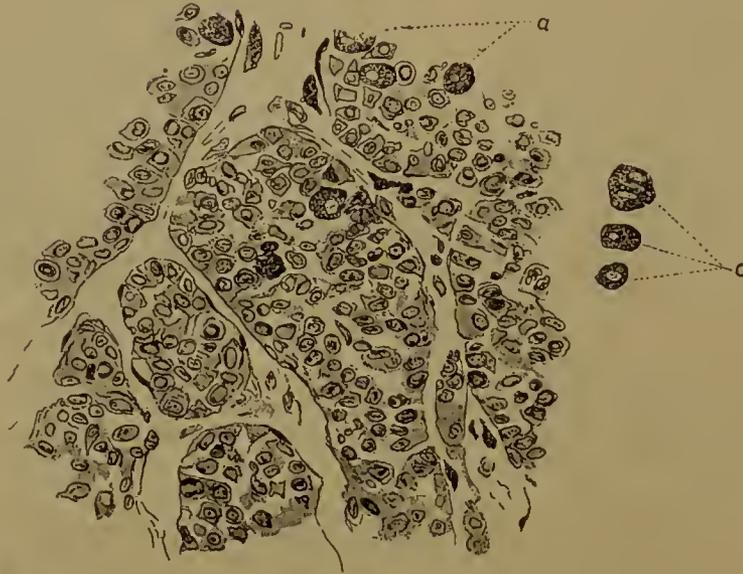
Section from an alveolar melanoma or chromatophoroma of the great toe.   The cells in general are here seen to be free from melanin granules, but these are present in occasional cells both of the tumor (*a*) and of the stroma (*b*).   At *c*, some of the melanin-containing cells are drawn separately.

Fig. 209

Pigment-containing cells from a spindle-celled melanoma.   (Ribbert.)

perfectly transverse, the masses appear oval or curved, and in any case there may be between them a good deal of cellular fibrous tissue. The whorls may show hyaline or calcareous change, in which last case the tumor is called a **psammoma.** The psammomas, sometimes multiple, appear to have always this endothelial origin and the rapidly growing ones are sarcomatous.

Lymphangio-endothelioma.—When there is no perfect whorling of cells around the capillaries, growths of this nature may be considered as arising from the endothelium of lymph channels.

Perithelioma.[1]—Tumors are sometimes found showing capillary channels cut in various directions, lined by endothelium, around each of which channels is a collection of cells, many layers deep, arranged radially. This arrangement in rows at right angles to the capillary axis is characteristic, and has led to the supposition that they arise from the endothelium of the perivascular lymph channel. The cells farthest from the vessel are evidently the oldest and probably from this cause are the most likely to degenerate; hyaline change in such areas gives perfect examples of the **cylindroma**—a term used to designate these and allied tumors that are formed of a collection of cylinders, each cylinder being a mass of cells surrounding a lumen, and themselves surrounded on the outside by a zone of hyaline change.

FIG. 210

Tumor of peritheliomatous type of the carotid gland: *G*, vessels; *Bl*, hemorrhage into a column of cells; at *d* the cells of the growth are taking on a more connective-tissue type; at *c*, hyaline degeneration.

Melanoma.—There is a great deal of uncertainty about these tumors, which are characterized by the presence of chromatophores, that is, cells which bear pigment, whether they be in the skin, the mucous membranes, or the choroid of the eye. These cells are found, normally, in the skin of the anal region or the pigmented areola of the breast, and exist in the pigmented warts that are so common on the skin. The pigment is melanin, an iron-free protein or protein derivative, often

[1] Many object to this term: it is permissible if understood as an abbreviation for "perivascular lymphangio-endothelioma."

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containing sulphur. We do not know surely if these cells are epiblastic or mesoblastic in their origin, whether they are epithelial or supportive in their nature, and some of the tumors are alveolar, suggesting a carcinomatous origin (Fig. 208), others, more particularly those arising from the choroid of the eye, are non-alveolar, with cells of the type of a spindle-celled sarcoma (Fig. 209). The tumors vary in color, from white (especially secondaries) to brown or black according to the amount of pigment present; they are highly malignant, and the secondaries are apt to be exceedingly abunbant. Microscopically, as above noted, the growths differ greatly. The most likely explanation of their varying properties is that one kind of cell, the chromatophore mother cell, of lymphangio-endothelial origin, gives rise under different conditions of vegetative activity to carcinoma-like or sarcoma-like tumors.

Other Tumors of Doubtful Relationship.—Cholesteatoma.—This is found especially related to the membranes of the brain, and is characterized by the presence of pearly nodules. The cells are of epithelial or endothelial type and among them may be cholesterin crystals. They are by most considered as endotheliomas, but the finding of hair follicles makes this not so clear. The name is, unfortunately, most commonly applied to a tumor found in the external auditory meatus and the middle ear, which is not a blastoma, but a condition allied to hyperkeratosis, an accumulation of flattened epithelial cells, which have not been cast off.

Tumors of the Carotid Gland.—The nature of the "carotid" gland being obscure, it might be expected that the nature of the tumors arising from it would also be obscure. These are at times like the peritheliomas and the sarcomas. Similar difficulty is found in the case of the coccygeal gland, and the perithelioma-like tumors that arise from it.

The Experimental Production of Malignant Growths. — Several observations have been made of late years upon the association between sundry occupations and practices, and the development of malignant tumors. Cancer of the lips and tongue associated with smoking clay pipes is an example. The most striking one is the frequency of epithelioma of the anterior abdominal wall in the highlands of Cashmir which obviously is co-related with the "khangri" basket. For warmth the inhabitants are accustomed to carry a basket or pot containing live charcoal suspended against the abdomen. Of occupational cancers the most noted are cancer of the scrotum which used to be common among chimney sweeps in Great Britain; the multiple epitheliomatous sores that are apt to develop in those engaged in the production of paraffin and coal-tar productions; and the frequency of similar epitheliomas connected with work in arsenic. The most recent and carefully studied example of this group of disturbances has been observed more particularly in connection with x-ray operators. Briefly, it is observed that while greater intensity of x-rays leads to cell destruction, in irritation of slighter grade coupled with fibrosis and capillary disturbances of the corium, there is the contrary process of extensive proliferation

of the epithelial elements. We may, indeed, say that now we can experimentally produce epithelioma by the action of x-rays.

Another interesting series of observations is that upon the relationship between protozoan and metazoan parasites, and the production of glandular carcinomas. Some few years ago Borrel called attention to the possible relationship between Acarus (the insect parasite causing scabies) and mammary cancer. Fibiger, of Copenhagen, has made an extraordinary study of cancer (epithelioma) of the cardiac portion of the rat's stomach (this is lined by squamous epithelium) and the presence of minute nematodes. Finding this worm imbedded in sections of more than one case of epithelioma of that organ, he was not satisfied until he had made out the life history of this particular parasite. Recalling that a similar form had been described in cockroaches, he discovered that in Copenhagen certain cockroaches (Blatta americana) were infected, whereas others (B. orientalis), were free. By feeding healthy rats upon infected cockroaches he was able to produce the cancer in a strikingly large portion of cases. What is more, he was able to infect the ordinary cockroaches, and then feeding rats upon them, he induced these large, very malignant epitheliomatous growths. We may connote his observations with those already noted—the tendency of protozoa like the coccidium, and metazoa like the bilharzia, to induce epithelial proliferation.

THE CAUSATION OF AUTONOMOUS NEOPLASMS.

It will be evident from the foregoing that some growths owe their origin to cell-rests; such are the teratomas and the teratoblastomas, the tumors originating from persisting rudiments of embryonic structures (gill clefts or branchial cartilages), and from cells displaced during the course of development (aberrant hypernephroma, columnar carcinomas in regions where squamous epithelium normally exists, etc.).

The idea of cell-rests has been known for long by Cohnheim's name, but, useful as it is, it gives no clue to the reason why tumor growth springs up from one cell-rest and not from another; even on Cohnheim's line we may go farther and say that new growths arise also from cells which have undergone *not congenital, but postnatal displacement*, as happens in squamous-celled carcinoma arising in a scar, or in columnar carcinoma from the edge of an ulcer. Thus Wilson more particularly has called attention to the fact that a large proportion of cases of gastric carcinoma originate from the edge of a healed gastric ulcer. But *cell displacement is not the essential*. Indeed, certain neoplasms arise from provedly undisplaced cells, and by actual transformation of the tissue cell into the tumor cell. Thus has been described the change of liver cells, the cell losing much of its nuclear chromatin and becoming granular with an enlargement of the nucleus, and a final acquirement of abundant protoplasm, no longer granular; and all this happens while the cell is

still connected to its fellows. This is the process we have referred to as undifferentiation or anaplasia. It is by a process of change like this that we can understand the hyperblastoses, which develop not from a single cell but by a generalized proliferation of the specific elements of a tissue, the cells showing all gradations from simple hypertrophy to pronounced malignancy. A general theory upon which to base neoplasia has been, for example, to consider it as the result of the removal of tissue restraint, while less widely reaching suggestions have been the attempts to show a parasitic origin for all neoplasms. All these factors may be present, but no one is adequate to explain all cases. An adequate explanation will have to show some influence always present in the cell itself, rather than an external stimulus or a series of external stimuli.

The Habit of Growth.—We have attempted to show that cell life is dependent upon the never-ceasing activity of exchange between nucleus and cytoplasm, between cytoplasm and food, between nucleoplasm, cytoplasm, and the detached ions that mean ferment action; energy can be expended in the direction of growth, of function, and of proliferation, the last occurring when a certain physiological degree of growth has been attained. If now cells be placed so that no function is demanded of them or permitted to them, while they continue to gain nourishment, they may remain vegetative or become vegetative, and acquire a habit of growth, losing the habit of function. The mere existence of immature cells or of cells that have passed from a differentiated form to a less differentiated form, is not enough; cells must assume this habit of growth and lose the habit of function before they can originate a neoplasm. A cell that is ready to be the starting-point of a neoplasm differs from an embryonic cell; the latter has the potentiality of differentiation still before it, the former has lost it. As suggesting how the cell has lost it, Oertel's hypothesis may be noted that as in the protozoa we find in some cells two nuclei, one associated with reproduction and the other with the functional activity of the cell, so in man and the metazoa there is chromatin of two orders, of which one governs the proliferative, the other the functional capacity of the cell. A tumor cell is a cell that has largely lost the latter; when lost the cell is unable to replace it. Such a cell can give rise only to daughter cells that lack this power of differentiation, but are still endowed with full vegetative properties. That such is the case is not yet proved, but the idea is worthy of preservation in the present state of our knowledge. It seems necessary to recognize among the blastomas some change in the biological properties of cells as an essential for neoplasia. It is not something outside the cell, neither an external stimulus nor a diminished external resistance; it may be that an external stimulus starts the cells on that path which leads eventually to their assuming neoplastic properties; it may even be that the malignant growth affords a secretion which depresses the vitality and inhibits the growth of surrounding tissue cells, but these are subsidiary. The essential point is that the cells giving rise to an

autochthonous new growth are so modified that the energy acquired by the accumulation of food is not discharged in the performance of function, as in the healthy cell in normal relationship, but is retained and accumulated only for purposes of growth and multiplication. This is far from denying that various stimuli assist the modification of the cell; it may be that in one case the cell's position, displaced as it is, tends to retard its function but not its vegetation, or in another case that a microbic or parasitic agent begins an inflammation that acts similarly, or in yet another case that a senile loss of function paves the way, the change being accompanied by an alteration in histological characters. There is not one specific agent, but many, and these at the most begin the process. The end-result is a cell mutation.

What is the practical bearing of this? It is that the cure of cancer does not lie in the discovery of a parasitic cause, for, judging by what we know of the nature of malignant cells the mere removal of a microbic or parasitic cause will not suffice to stop cell activity and the propagation of the properties that the cells have assumed. We have rather to seek agents that will influence the growing powers of these cells. Two possibilities, at least, lie open.

The first of these is an apparent parallel to bacterial immunity. In the inoculation of mouse cancers, it has been found that successful inoculation with a cancer is followed by subsequent failure to inoculate again the same mouse; two simultaneous inoculations may be successful, but if one be successful, a subsequent inoculation fails. Some such inoculated tumors subsequently shrink and disappear, and the animal is immune to inoculation with the same or an allied tumor. These phenomena are evidently due to the production of antibodies by the tissues, parallel to that seen in various infections, and it seem possible that tumor or even normal cell extracts might exalt the defences of the body against tumor growth. Yet we must not be blind to the fact that many inoculable tumors induce but a very slight general reaction.

The second mode of destruction of new growths is parallel to the employment of the agents that produce passive immunity. It may be that drugs or animal substances, or mechanical agents like radium or the Röntgen rays, chemicals such as salts of selenium and tellurium, or body ferments may be found, to which the neoplastic cells are more sensitive than are the normal cells, their growth being arrested and atrophy and absorption ensuing. As a matter of fact it has been fully demonstrated that radium and x-rays especially arrest the activity of vegetative cells. Wassermann has announced partially successful inoculations with compounds of selenium and tellurium with anilin dyes: these have resulted in the destruction and disappearance of the cancer cells in mouse carcinoma without injury to the tissues in general. We say partially successful: the experiments were wholly successful in the case of small tumors; with larger growths, while the tumors disappeared, the animals died, apparently poisoned by the products of tumor-cell disintegration.

CYSTS

A cyst is a sharply limited, abnormal collection of fluid unprovided with a channel of outflow, possessing a well-developed boundary wall. It is round or oval, and the fluid fills it. We do not count the serous cavities as cysts if they contain fluid, although we regard those serous sacs, called bursæ, as cysts if they contain a marked excess of fluid over the normal amount. Cysts are tumors only in the sense that they are swellings; they are in no sense neoplastic, and the wall grows in direct relationship to the amount of the fluid content, and the tension exerted by it.

According to their causation, cysts may be divided into the following groups: (1) **retention**

Fig. 211
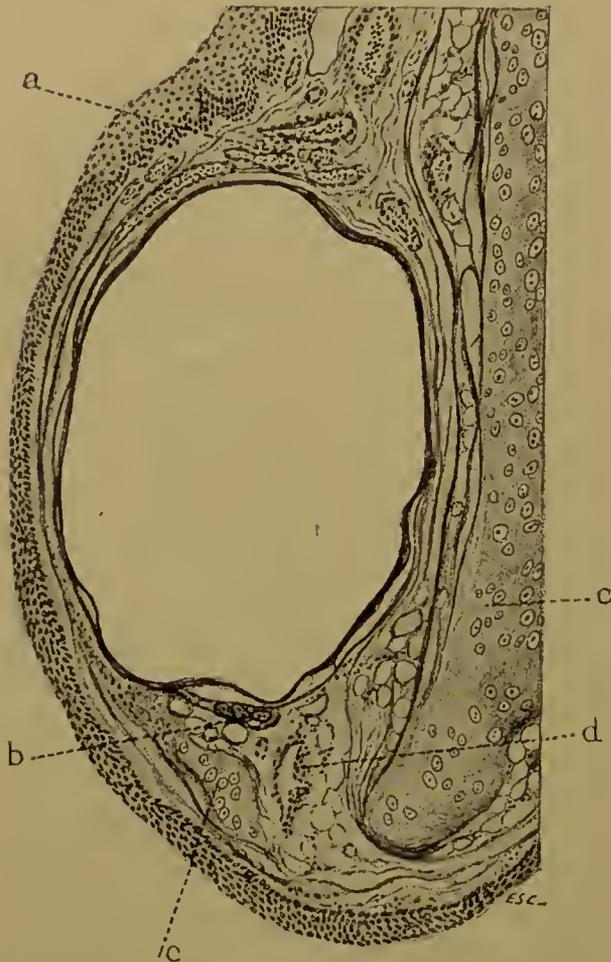
Section through a retention cyst of mucosa of under aspect of epiglottis, due to obstruction of a mucous gland. (Professor Klotz) (low power.) *a*, blood vessels; *b*, compressed acini of a mucous gland; *c*, cartilage; *d*, artery.

Fig. 212
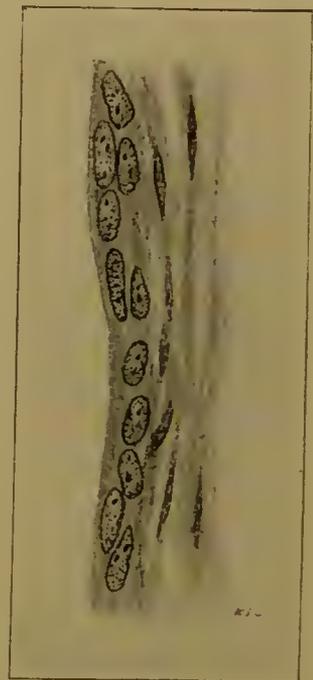
From the same section under higher magnification to show the flattened epithelium lining the cyst.

cysts, due to abnormal dilatation of preëxisting cavities of the organism as a result of secretion outstripping absorption; (2) **hemorrhagic** cysts, due to escape of blood into the tissues and subsequent encapsulation; (3) **necrotic** cysts, due to the death and liquefaction of tissues with subsequent encapsulation; and (4) **parasitic** cysts, due to the development (in itself normal) of metazoan parasites within the organism, such parasites possessing a cystic stage.

A. **Secretory or Retention Cysts.**—This group may be subdivided according to the nature of the cells lining the cysts into (1) cysts with

cubical or columnar "glandular" epithelium, (2) endothelial, (3) ependymal, (4) squamous epithelial, and (5) composite cysts.

In all of these, when cellular activity leads to secretion into a cavity unprovided with an outlet or when the outlet is obstructed, the fluid is secreted against pressure, which, while low, is above that in the capillaries; as the secretion is continuous and the absorption less rapid, the cavity is gradually distended, and under this gradual, not excessive strain, cell multiplication is favored, and not only the lining cells multiply but also the underlying connective tissue. Eventually the lining cells become flattened by pressure, (Fig. 212), and ill-nourished by reason of the pressure on the vessels in the walls, so that atrophy and final disappearance may result. The watery contents of the cell are absorbed, so that the less diffusible products of secretion become more and more concentrated, until the cyst may be filled not with watery fluid but with inspissated, thick, jelly-like, or colloid content.

I. Of Antenatal Origin.—*Congenital Cysts Due to Persistence of Parts of Embryonic and Fœtal Ducts.*—This is a large group. In the growth of the embryo and fœtus, certain passages that ordinarily become closed and atrophy, may not become completely absorbed; these remain isolated in other tissues, and either immediately, or after years have elapsed, their cells may take on secretory activity, giving origin to cysts. Some of these are as follows:

(*a*) **Thyrolingual cysts** in the median line of the neck, from the thyrolingual duct leading down from the *foramen cæcum* of the tongue to the thyroid.

(*b*) **Branchial cysts** on the side of the neck, between the angle of the jaw and the sternoclavicular articulation, from the branchial clefts. The contents of this series vary from mucous fluid to sebaceous material according to whether they originate from the inner end, lined with mucous membrane, or the outer end, lined with squamous epithelium.

(*c*) **Vitello-intestinal cysts**, near the navel, from the omphalomesenteric duct which communicated between the small intestine and the yolk sac.

(*d*) **Urachal cysts**, in the hypogastric region, from persistence of parts of the urachus.

(*e*) *Cysts of the Primordial Genito-urinary Passages in the Female.*— Fig. 213 will serve to recall the relations of these ducts and the changes by which they arrive at their finally destined purpose; cysts are liable to arise from unabsorbed portions of those that atrophy. **Cysts of the Wolffian body** are apt to be multilocular, growing in the broad ligament. Cysts arise from the lateral (free) tubes of the paroöphoron; they are of small size. The cysts that arise from the connecting tubes of the paroöphoron (connecting with the ovary) may be of large size; they are often single, and are lined by various kinds of epithelium, though this may be lacking in the larger ones, where also cholesterin may be found. **Cysts of Gärtner's duct** occur in the broad ligament and in the

vaginal wall. **Hydatid of Morgagni** is the term which describes the cystic dilatation of the long fimbria of the Fallopian tube.

(*f*) *Cysts of the Primordial Genito-urinary Ducts in the Male.*— **Stalked hydatids** are found at the upper pole of the testis arising from Wolffian tubules. **Encysted hydrocele** of the testis may arise from the vasa efferentia, while from the Müllerian duct may arise at its distal end a **sessile hydatid**, a cyst in connection with the globus major of the epididymis.

FIG. 213
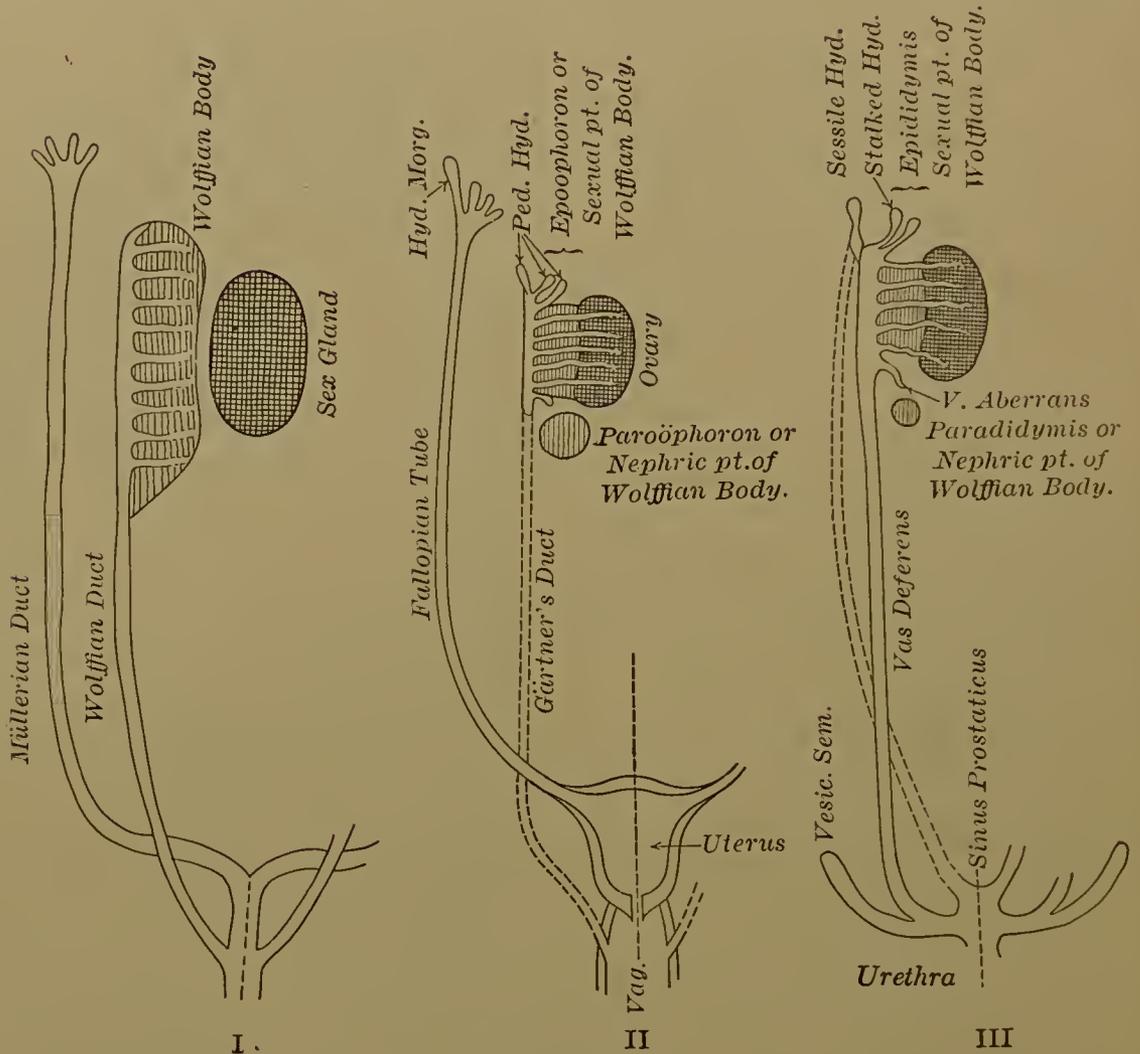
Relationship of the sexual ducts and their rudiments in the two sexes: *I*, the indifferent primary type. *II*, the differentiation in the female. *III*, the differentiation in the male. *Hyd Morg.*, hydatid of Morgagni. *Ped. Hyd.*, pedunculated hydatid. *Vag.*, vagina; *Sessile Hyd*, sessile hydatid.

(*g*) *Congenital Cysts Due to Arrested or Imperfect Development of Glandular Organs.*—This class is well exemplified by the **congenital cystic kidney**. In the formation of this organ, the glomerulus and the tubule proper arise from the mesoblastic nephrogenic tissue, while the collecting tubules take origin from the Wolffian duct. When a proper junction between the tubules from these two sources fails, the secretion from above distends the upper parts of the tubules and cysts result.

II. OF POSTNATAL ORIGIN.—1. *Originating in Tubular Glands through Obstruction of their Ducts.*—These are the ordinary "retention"

cysts, arising from plugging of the duct by mucus, or a calculus, or from stenosis of the duct from previous injury or by the pressure of surrounding fibrous tissue or of near-by new growth. Examples are very numerous; **ranula** of the floor of the mouth from obstruction of the sublingual duct or that of the *glandula incisiva* somewhat in front of it; **salivary cysts** from blocking of a salivary duct; **mucous cysts** of the intestinal mucosa from blocking of the crypts; pancreatic cysts (**ranula pancreatica**); cysts of the mucous glands of the epiglottis, the trachea, of Cowper's glands, and the glands of Bartholin; bile cysts of the liver; cysts of the kidney, of the bladder mucosa, of the glands of the cervix of the uterus (**ovula Nabothi**), of the lacrimal gland (**dacryops**), of the ducts of the mammary gland (**galactocele**); **wens** and sebaceous

Fig. 214
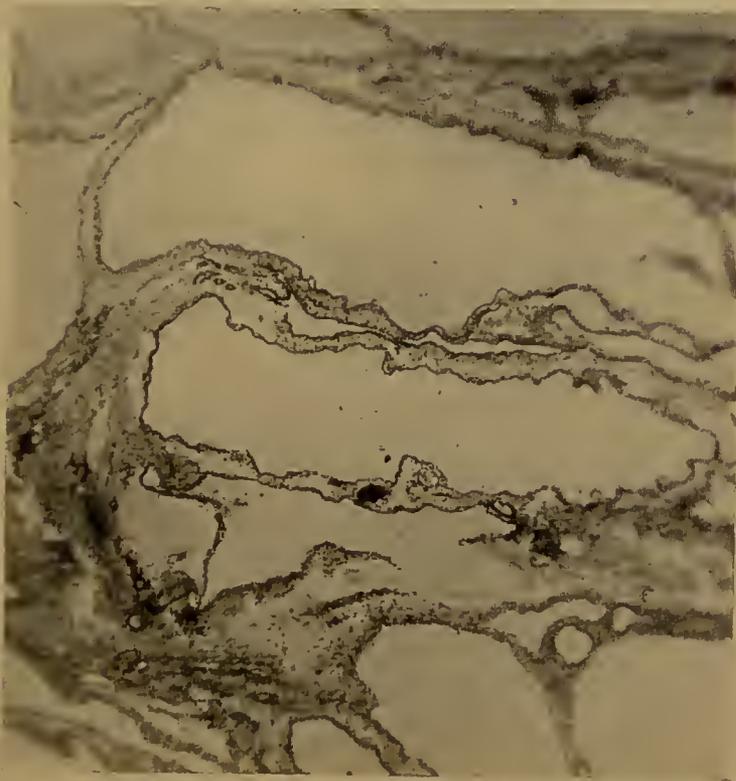
Congenital cysts of the kidney from a newborn child dying shortly after birth. Each organ, greatly enlarged, consisted of an agglomeration of elongated cysts as shown here. (From the collection of the Royal Victoria Hospital. Zeiss objective DD without ocular.)

cysts of the skin. Here also belong cystic dilatations of hollow organs, such as the gall-bladder (**hydrops vesicæ felleæ**), of the appendix, and the Fallopian tube (**hydrosalpinx**); the retention of uterine discharges by occlusion of the cervix gives **hydrometra**.

2. *Originating in Ductless Glands.*—Glands like the thyroid and pituitary, being formed of closed vesicles, are liable to distension of these vesicles, so that thyroid cysts (**thyroid goitre**) or pituitary cysts occur; and in the ovary, cysts of the Graafian follicles and cysts of the corpora lutea may arise. In some of the former an ovum may persist, though generally it undergoes disintegration.

III. OF NEOPLASTIC ORIGIN.—1. **Cystadenomas.**—Adenomas of tubular glands by the continued production of (abnormal) secretion become distended and cystic; especially is this true in the ovary and the mammary gland; and in such cysts there is a tendency to the multiplication of the lining membrane, so that papillomatous ingrowths of great complexity occur. It will be readily understood that here the borderline of pure proliferation is readily passed and neoplastic growth, even of a carcinomatous nature, instituted.

2. **Endothelial Cysts.**—The second group of cysts (classified according to the nature of the lining membrane) is a relatively small one. The best examples are serous cysts—sacs distended with serous fluid or

FIG. 215
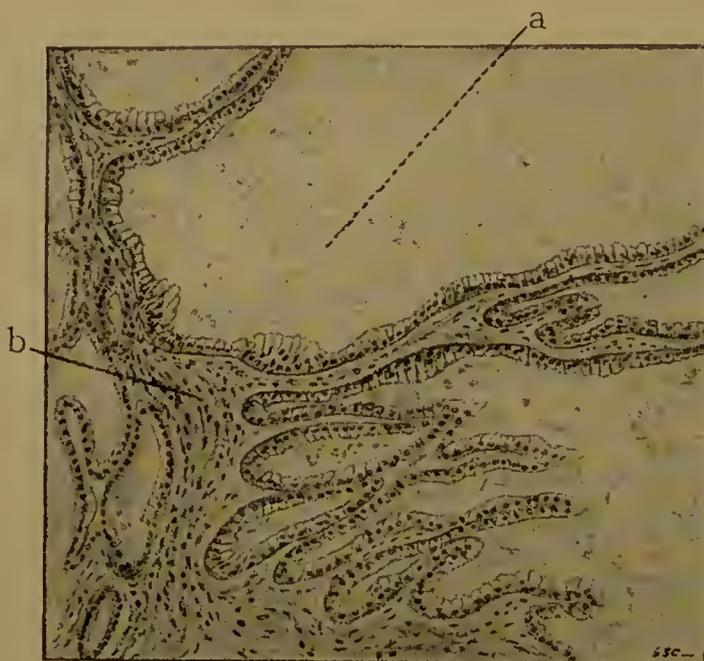
Section through a portion of a large multilocular ovarian cyst (*cystoma papilliferum*), showing cysts of various sizes lined by columnar epithelium, some large, as at *a*, others small, others with papillary ingrowths; *b*, fibrous stroma.

lymph. These sacs are normally lined by endothelium, either of a cut-off portion of a serous cavity or of the lymphatic system. Examples of the former are **scrotal hydrocele** and **cysts of the canal of Nuck,** of the latter, **bursal cysts,** and **"ganglia"** (cysts formed by the cutting-off of hernial protrusions of the synovial lining of the tendon sheaths). Bursal and lymph cysts in general owe their origin to a combination of circumstances; there is increased activity and lessened absorption, and in many there is no doubt a low grade of inflammation, which, tending to a progressive thickening of the wall, yet further interferes with the proper degree of absorption.

Of serous cysts of congenital origin the most striking are the **hygromas,** which are most common in the neck (hygroma colli). Yet the hygroma is generally not a simple cyst but by reason of plentiful endothelial reproduction may be recognized to be a lymphangio-endothelioma.

3. **Ependymal Cysts.**—Imperfect development, or intra-uterine inflammation leading to stenosis, may cause a localized closure of some part of the spinal or cerebral canal, or of the channels of communication between that canal and the external lymphatics. Either happening will lead to accumulation of cerebrospinal fluid and cystic dilatation of the ventricles or of the spinal canal, giving rise to **hydrocephalus internus, hydrocele of the fourth ventricle**, or cysts of the spinal canal such as **syringomyelocele** (to be distinguished from cystic states of the meninges). A snaring off of portions of the ependyma during development may lead to the appearance of simple cysts in the gray matter; they may be lined by a ciliated epithelium.

4. **Squamous Epithelial Cysts.**—As already noted, the cysts lined by squamous epithelium and having sebaceous contents may show themselves on either side of the neck, as the outcome of persistence of the outer epithelial portion of one or other branchial cleft. A fairly common form of acquired epithelial cyst is met with in the fingers of sewing women, and, more rarely, as the result of other forms of trauma. As the result of small portions of the epiderm becoming driven into the deeper tissues, the cells persisting grow into a globular mass, the actively proliferating cells being on the outside, the cell debris accumulating within, as indicated in Fig. 216.

FIG. 216
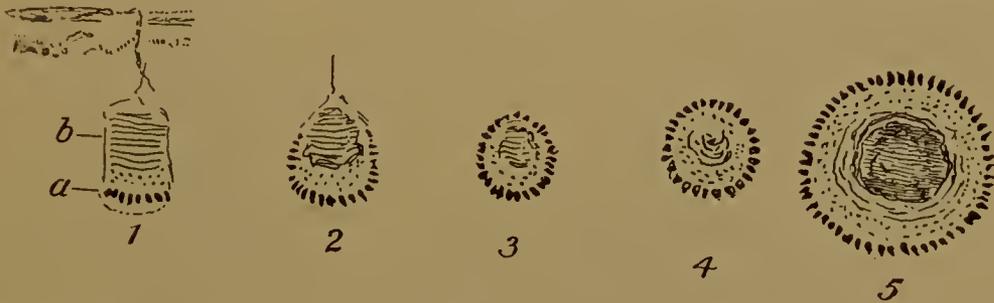
Diagram to illustrate mode of formation of an implantation cyst of skin: 1 shows a fragment of skin depressed into the underlying tissues; the actively growing cells of that fragment are upon its under aspect at *a* (the palisade layer of the rete Malpighii); the stratified flattened cells of the epidermis (at *b*) have lost the power of growth; 2 and 3 show the continued growth of the cells of the rete Malpighii, which from the want of growth of the cells at *b* must come to surround those cells, and form as at 4 a solid, and later, as at 5, a hollow sphere.

5. **Composite Cysts.**—These are cysts whose walls are composed of more than one kind of epithelium, whose contents are from glands discharging into the cyst; **sequestration cysts** of the skin are such, as is **hydronephrosis**.

Sequestration cysts occur in the line of fissures of the body, where in the process of joining, some cells of one or both surfaces become depressed, and sequestered in the underlying tissue, there eventually giving rise to a cyst. This may occur at the dorsal groove, the thoracic-abdominal cleft, or the facial clefts, and in the part cut off there are generally sweat or sebaceous glands, and hair follicles, which determine the nature of the cyst contents. Such cysts may not only be superficial

but deep, and because of the comparatively late development of the skull, they may be found attached to the dura mater. Hydronephrosis occurs when the urinary passage is obstructed; the kidney continues to secrete, and the urinary canal to be distended, especially the pelvis

Fig. 217

Diagram of an Echinococcus hydatid: *cu*, thick external cuticle; *pa*, parenchymal (germinal) layer; *c, d, e*, development of the heads according to Leuckart; *f, g, h, i, k*, development of the heads according to Moniez; *l*, fully developed brood capsule with heads; *m*, the brood capsule has ruptured, and the heads hang in the lumen of the hydatid; *n*, liberated head floating in the hydatid; *o, p, q, r, s*, mode of formation of secondary exogenous daughter cyst; *t*, daughter cyst, with one endogenous and one exogenous grand-daughter cyst; *u, v, x*, formation of exogenous cyst (after Kuhn and Davaine); *y, z*, formation of endogenous daughter cysts (after Naunyn and Leuckart); *y*, at the expense of a head; *z*, from a broad capsule; *evag.*, constricted portion of the mother cyst. (R. Blanchard, slightly modified.)

of the kidney, so that ultimately the kidney itself may be transformed into a thin-walled sac. Of the nature of composite cysts, too, are those inclusions of tooth sacs or remains of the enamel germ that are found in the jaw. These may be lined by epithelium, and may even have teeth projecting into them, in which case they are true **dentigerous cysts.**

B. **Hemorrhagic Cysts.**—In the brain, as a good example, we find cyst formation following upon a hemorrhage; the blood outpoured acts as a foreign body and the tissue makes an attempt to wall it off by a fibrous capsule, while at the same time leukocytes and autolysis

Fig. 218
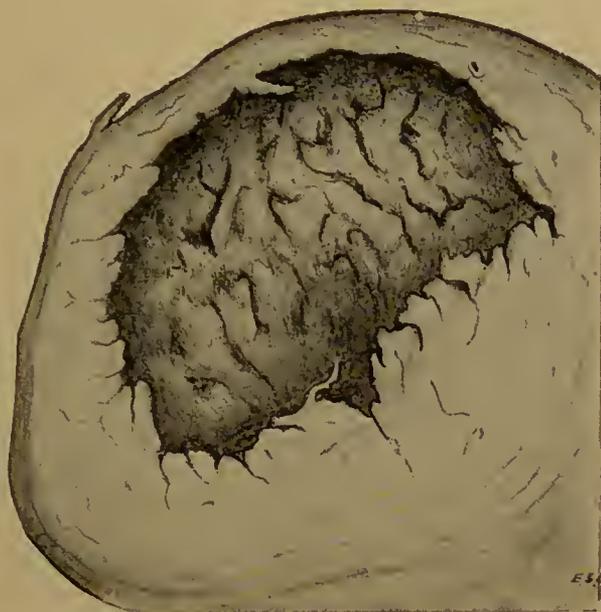
Necrotic cyst of liver due to necrosis and autolysis of the central region of a secondary carcinomatous nodule.

are responsible for the removal of the corpuscles. The blood pigment, too, is gradually removed, so that a small amount around the capsule may be the only indication of the fact that blood has been present, and even this ultimately disappears. The cyst finally contains a clear, serous fluid. A like process occurs in the goitrous thyroid and in the scalp of the newborn (**cephalhematoma**), and sometimes in the corpus luteum, although the metamorphosis of the last-named has, of course, a much deeper significance than the mere formation of a cyst.

C. **Necrotic Cysts.**—Wherever there has been a necrosis of tissue without infection, as in a large infarct, it may happen that, after the tissue has become liquefied by autolysis, the soluble products diffuse out, the lymph diffuses in, and a cyst is formed. Such a formation may be seen in the centre of a large cancerous nodule.

D. **Parasitic Cysts.**—Certain metazoan parasites pass one cycle of their existence in a cyst within the tissues of their host. Those occurring most notably in man are *Tænia echinococcus* and *Trichina spiralis*, the cysts of the latter being very small, containing each a coiled-up individual trichina. The cysts made by the former are, however, of large size, and occur most often in the liver, although many other organs may be found to contain them. The wall of the large cyst is supplied, in part, by the parasite, although the irritation of its presence leads the surrounding tissue to build a fibrous capsule on the outside of the hyaline cyst wall proper.

This so-called **hydatid cyst** may be single or multiple; its wall is hyaline and laminated, lined internally by a granular (cellular) layer from which project the heads of new individual parasites, with characteristic hooklets. Secondary heads are constantly being budded off

Fig. 219
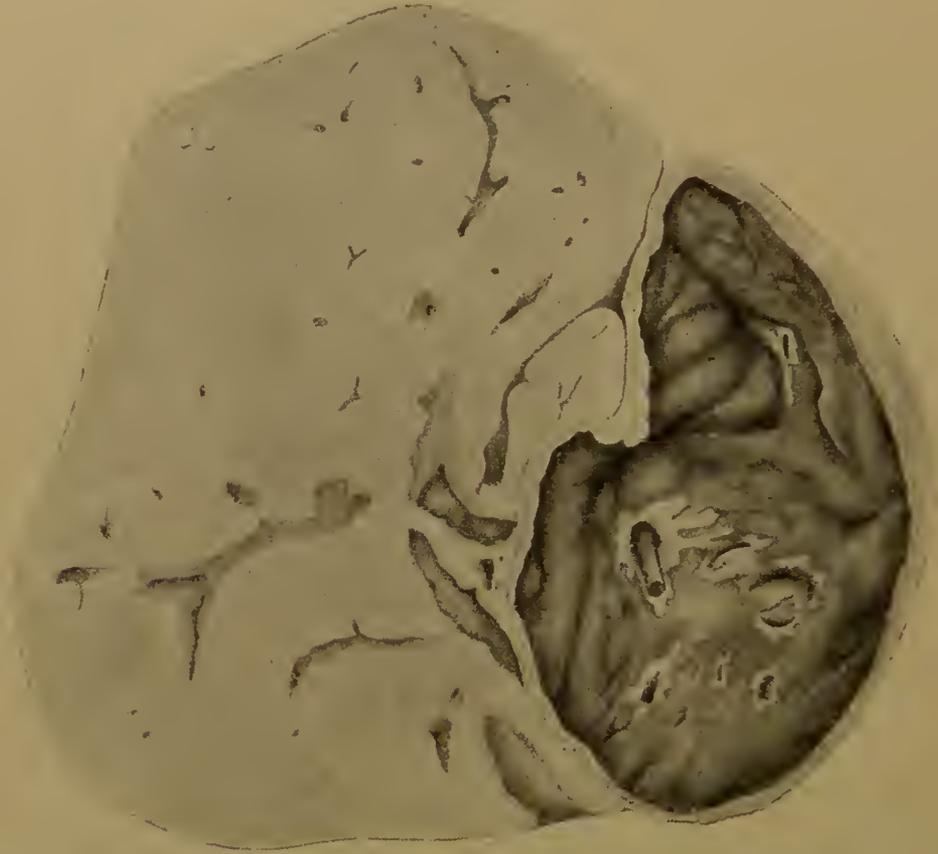
Echinococcus cyst of liver. The sound leads into a branch of the hepatic duct, by which the infection made its way into the liver tissue. (Chiari.)

from the wall and thrown into the fluid; these it is which render the fluid likely to infect the peritoneum if allowed to come in contact with it during removal. The secondary heads may give rise to the formation of daughter cysts in the primary sac, or less frequently, the daughter cysts may form on the outside of the mother cyst instead of the inside, causing a multilocular cyst.

PART II

SPECIAL AND SYSTEMIC PATHOLOGY

CHAPTER VII

THE CARDIOVASCULAR SYSTEM

FROM the discussion of the general effects of morbid agencies upon the cell and the tissues, we now proceed to take into review the organs and systems; pass, that is, from a consideration of what is usually known as General Pathology to that of Special, or, as we prefer to term it, Systemic Pathology. Our object as pathologists is not merely to become familiar with the various lesions that may affect each special organ, but, realizing always that pathology is the handmaid of clinical medicine, to keep in mind how these lesions of particular organs modify the function of the systems of which those organs form a part, and so modify the activities of the body as a whole. It is of peculiarly little value to the practitioner when, for example, he has diagnosticated a case of exophthalmic goitre to be able to call to mind the picture of the

thyroid changes that occur in this disease, unless with this he simultaneously appreciates what those changes imply, namely, increased activity of the thyroid cells, increased discharge into the blood of thyroid secretion, increased oxidative changes, and metabolic activity throughout the organism, etc. The use of pathology, in short, is to explain the phenomena of disease, and with this to afford indications for rational treatment, and while the mass of data with which the student should be familiar is so large that our treatment of systemic pathology must be painfully epitomized if everything is to be brought within the covers of a single volume, we shall throughout conscientiously endeavor to keep before our readers this broader and more practical aspect of our subject.

Our study of the pathology of the cardiovascular system includes, first, that of the circulation medium, the blood (and lymph), and, second, that of the apparatus whereby this medium circulates.

In considering the circulatory fluid we are apt to lay too little stress upon the cell juices and the lymph. The text-books of anatomy do not lay stress upon them, save to describe the larger lymph ducts: yet this slowly circulating fluid represents perhaps two-thirds of the body weight. If we consider a human body weighing one hundred and fifty pounds in life, the same body perfectly mummified and dried weighs, at a venture, thirty or forty pounds: of the remaining hundred and more, the circulating blood supplied perhaps eight, and the rest is lymph and tissue juice. The relationship of this slowly moving mass of fluid to the circulating blood will be understood if we use the example of a river which widens out into a marsh. Here and there are streams which run with a perceptible current, comparable to the blood and lymph in vessels, but the greater part of the surface of the marsh is bathed in water which appears stagnant, but which, nevertheless, is in actual contact with the currents and is thereby slowly replaced and renewed. This great mass of slowly moving marsh water is comparable to the lymph.

We are too apt to say in a poll-parrot manner, that all the tissues gain their nourishment from the blood, and saying this to forget that, save in the case of leukocytes, which are suspended in the blood, and those other cells which line the bloodvessels, this statement is incorrect, giving us a false mental picture of what really happens. Save in the case of the above-mentioned exceptions, the tissue cells gain their nourishment from the lymph. This, it is true, is derived from the blood. It is, however, not identical with the blood plasma; its composition varies in different organs and regions and in different states of the body; the indications are that its transfusion from the vessels is largely a governed process, varying according to circumstances, while it receives primarily those products of cell activity which are not directly excreted by the glands. The lymph, then, rather than the blood, is the great medium of interchange. Just as the lymph originally is derived from the blood, so sooner or later it is discharged into it again.

We have to deal with:

I. The blood.
    1. Quantitative alterations:
        (1) In the amount of blood as a whole.
        (2) In the amount supplied to particular regions.
        (3) Disturbances in blood supply brought about by:
            (*a*) Hemorrhage.
            (*b*) Intravascular disorganization of the blood (thrombosis).
            (*c*) Effects of foreign bodies (embolism).
    2. Qualitative alterations:
        (1) In the fluid menstruum of the blood.
        (2) In the corpuscular elements.
II. The lymph.
    1. Quantitative changes;
    2. Qualitative changes.
III. The blood-forming organs.

It will, however, be more convenient, as it is more in accordance with custom, to discuss the blood-forming organs after we have treated the cardiovascular apparatus.

THE BLOOD

Quantitative Alteration.—It needs but a short experience in the post-mortem room to realize that in disease the relative amount of blood in the body varies within very wide limits. Some bodies are strikingly dry, others (notably cases of chronic obstructive heart disease) ooze abundant blood at every cut. But in health also there is wide variation. This is demonstrated by Haldane and Lorrain Smith's method. Carbon monoxide is taken up by the red corpuscles with much greater avidity than is oxygen. If, therefore, an individual be made to breathe for a short time a known amount of carbon monoxide, it is easy, by removing after a few minutes some cubic centimeters of that individual's blood, to estimate the amount of carbon monoxide per cubic centimeter in that blood, and therefore the total number of cubic centimeters of the circulating blood. The usual statement is that the amount of blood corresponds to one-thirteenth of the body weight. This is too high. The average amount is rather under one-twentieth, but while this is so, a robust young athlete may have twice as much blood per kilo of body weight as has his wiry grandparent, although both appear to be in perfect health.

These facts put us on our guard regarding the value of specific gravity determinations and red corpuscle counts. The same results as regards heightened specific gravity or increase in the number of erythrocytes may be produced equally by an increased production of corpuscles, and, on the other hand, by reduction in the fluid of the blood. The same is true, *mutatis mutandis*, with regard to lowered specific gravity, or decrease in the number of corpuscles. Without a determination of the amount of circulating blood, enumeration of the

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corpuscles gives us no sure information regarding variation in the production or destruction of the corpuscles. Indeed, with this fuller knowledge we are beginning to find out that conditions which hitherto have been classed among the anemias, or states of insufficient blood production, are truly conditions of hydremia, or dilution of the blood and actual increase in its amount. There exist, that is, states of true oligemia, or diminution in the amount of circulating blood, and of plethora or increase in the blood volume.

Oligemia (Ischemia).—This diminution in volume may be found in some secondary anemias and in pernicious anemia. In these conditions we find at autopsy not only that the blood is thin and of a pale color, but that the amount of the blood in the heart and vessels is notably small. Like reduction in quantity may follow extreme or repeated hemorrhages or, again, great loss in the fluid part of the blood, as occurs in cholera and pernicious vomiting. In this latter case the fluid left in the vessels may be thick and tarry, owing to concentration of the corpuscles, contrary to what occurs after extensive hemorrhage, when what blood there is is singularly pale and thin, owing to the passage into the vessels of tissue fluids, in order to make up for the loss of blood proper.

Plethora.—Adequate nutrition, with active development of the muscular system, is found to be associated with increase in the amount of blood above the normal. There is thus, contrary to the teaching that has prevailed for some years, such a condition as **simple plethora**. With this also exists pathological plethora, as seen in obstructive heart disease, where the blood is apt to be darker than normal, owing to imperfect oxidation, although estimation of its specific gravity shows that it is more dilute than normal (**hydremic plethora**). We do not wholly understand what are the conditions that lead to this hydremic state in heart disease. A similar condition has also been noted in cases of obstructive lung disease. A somewhat different type is the plethora that follows the daily consumption of many liters of light beer, allied with the so-called Munich beer heart. In these cases the heart is found much hypertrophied and dilated, clearly in response to the larger amount of fluid which is absorbed from the alimentary canal in successive tides, necessitating increased work to pump the increased volume. Yet another form of plethora is seen in chronic Bright's disease, attributed by some to reduced discharge of water through the damaged kidneys, by others to retention of chlorides in the tissues and the associated necessity of increased fluid for their due solution. Here, also, there is a heaping up of lymph and fluid in the tissue spaces (**anasarca**).

Alteration in Distribution Due to Cardiac Disturbance.—It is obvious that, the blood being kept in motion by the heart, disturbances of that organ materially affect the quantity of blood in the veins and arteries respectively. These disturbances may be broadly divided into three orders: (1) those involving the heart muscle; (2) those of the valvular apparatus; and (3) those of the nervous mechanism controlling the heart beat. By each and all of these the pumping action of the heart may be modified.

Disease of the heart muscle leads to weakening of the same, so that the organ is incapable of propelling the adequate amount of blood either from the right ventricle through the lungs into the left heart, or from the left ventricle into the systemic arteries. Similarly, imperfect action of the valves results either in direct obstruction to the inflow of the blood through the narrowed orifices, or to indirect obstruction, from regurgitation of blood already forced forward, through valves that are incompetent and patent when they ought to be closed. In both orders the result is an arrest of the inflow of the blood with, as a result, a progressive accumulation of blood on the venous side of the heart; overfilling of the veins, whether of the lungs alone or of both lungs and the various organs; relative deficiency in the arterial blood supplied to the various organs, and lowering in the arterial blood pressure. The effects of this we shall discuss under the heading of Passive Congestion (p. 420). Where the left ventricle or valves of the left heart are involved, the pulmonary veins exhibit distension and increased pressure with congestion of the lungs and all its attendant disturbances of respiration. This throws increased work upon the right ventricle, which undergoes hypertrophy and dilatation, and eventually, the right heart becoming unable to overcome the obstruction, there results also congestion of the systemic venous system.

Disturbance of the cardiac nervous system, whether acting more particularly upon the vagus paths, the accelerators, or the intrinsic nervous mechanism, leads to alterations in the frequency or the regularity of the heart beat. **Tachycardia,** or increased rate of beat, may eventually lead to heaping up of blood in the systemic veins in consequence of shortened diastole and imperfect filling of the ventricles. **Bradycardia,** or slowing of heart beat, may lead similarly to defective filling of the arteries with resultant accumulation of blood on the right side of the heart.

Alterations in the Distribution of the Blood Due to Disturbances Affecting the Vessels.—The vascular tree is so extensive that it is capable of holding very much more than the normal amount of blood; the vessels of the liver alone fully distended are said to be capable of holding the whole of the circulating blood. Thus, for the circulation to continue, it is essential that the vascular channels be reduced down to such a width and extent that the normal amount of blood fills them. This is brought about by two main agencies, namely, arterial contraction (tone), and muscular tone, the compression exerted by the partial contraction of the muscles in general and notably those of the abdominal wall. The existence of muscle in the walls of the veins shows that these also are capable of variation in caliber. The recent researches of Yandell Henderson demonstrate clearly the existence of a venopressor mechanism. It follows that, by the action of one or other factor, the blood may find itself in relative abundance on the arterial side of the circulation or on the venous, although the close interaction between the heart and vessels may bring it about that opposed states of the arteries may result in the same general effects upon the distribution

of the blood. Extreme contraction of the arteries and arterioles, for example, may result in an obstructive heaping up of blood on the right side of the heart, but so also extreme dilatation of the arteries and arterioles may be followed by such a lowering of the blood pressure that the circulating fluid cannot be forced through the veins, but, stagnating there, affords a similar picture of passive congestion. We have already discussed the effects of vascular relaxation, when treating of Shock and Collapse (p. 182).

Local Alterations in Blood Supply.—Increased activity of an organ or part is, as is well known, accompanied by increased passage of blood to the same. Such increase is largely determined by the vasomotor apparatus, although at the same time there are indications that the reaction of the lymph in the part has a direct influence upon the musculature of the vessels. The lymph may become more acid with activity of the tissues and, further, may come to contain other diffusible cell products capable of acting on the vessel wall. Many other influences determine the arterial supply of a part, as again the passage of blood out of it through the veins. We thus recognize the following states:

1. (Local) active hyperemia, due to increased determination of blood to the part through the arteries.

2. (Local) passive hyperemia, due to obstruction to the discharge of blood through the veins.

3. (Local) capillary hyperemia, in which, with no change in the caliber of the artery and no obstruction to the outflow, a hyperemia is induced by widening of the abundant capillary channels of an organ.

4. (Local) anemia.

Active Hyperemia of a part may be **direct**, due to dilatation of the arteries supplying that part, or **collateral**, due to contraction of other arteries whereby the blood pressure is raised, and as a result more blood is poured into those arteries which are not actively contracted. This latter we see in the development of a collateral circulation in a limb or other region after obstruction of the main artery. The direct form is brought about either by stimulation of the vasodilators (**neurotonic hyperemia**), a paralysis of the vasocontractors (**neuroparalytic hyperemia**), or direct local action of physical or chemical agents on the part (warmth, diminution of external pressure, after-results of temporary ligation, atropin, croton oil, etc.). Such arterial hyperemia is characterized by increase in size of the affected part, bright red color, increased warmth with, it may be, throbbing and pulsation.

Capillary Hyperemia is usually classed as arterial. We are, however, inclined to hold that the "active" hyperemia of inflammation is due not so much to dilatation of the arteries going to the inflamed part, as to physical changes occurring in the capillary area whereby the onflow of the blood is hindered. In all viscera possessing muscular walls or capsule, expansion of that muscle and lack of tone of the same, passively permit a dilatation and hyperemia of the capillaries within the viscera.

Venous Hyperemia or Passive Congestion.—Obstruction to the onflow of the blood or closure of a vein necessitates that the blood propelled

from the artery accumulates behind the point of arrest, unless, that is, there be so extensive a collateral network of veins that the blood can escape through these. If, however, the obstruction is beyond the point where the veins of a part converge, then accumulation must occur. If, for example, the obstruction occurs in the right heart the whole systemic venous system is apt to show the condition of passive congestion. If, again, the obstruction is in the left heart the whole pulmonary area becomes intensely congested. Thus (1) cardiac weakness, (2) hindrances to perfect inspiration, as from paralysis of the diaphragm or accumulation of fluid in the pleural cavity, and (3) arterial dilatation with lowered blood pressure, all lessen the onflow of the venous blood, and, to a greater or less degree, favor venous congestion. Such overfilling of the veins tends to show itself, more particularly, in those regions in which the veins receive little support from their surroundings. It also must be remembered that a forward passage of blood through the veins is aided by muscular contraction, as again by the negative pressure on the thorax during inspiration, and lack, or relative lack, of these is also a factor favoring local or general congestion. It is, however, where there is obliteration of the venous channels that the passive hyperemia is apt to be most marked.

As a result of this damming of venous blood in a part (1) it becomes enlarged in consequence of the increased amount of contained blood, and, secondarily, as a result of increased transudation from the distended capillaries; (2) it becomes of a dark purplish color, owing to the distension of those vessels whose blood, by long continuance in them, has become intensely venous, and (3) where superficial, the part is cooler than the surrounding parts, owing to the slowed circulation and increased radiation. The blood may become intensely venous, and this explains the **cyanosis** of sufferers from passive congestion. The vessel walls are apt to show evidences of malnutrition, the epithelium becomes abnormally stretched, and may exhibit fatty degeneration, and, as a result, there is increased transudation into the tissues, resulting in **œdema.** Where there is venous congestion of large areas, as in heart disease, this œdema is one of the most striking features. There may be accumulation of fluid in the body cavities (**ascites, hydrothorax**), and in the subcutaneous tissues (**anasarca**). Perhaps the most rapid accumulation of fluid takes place when the portal vein becomes blocked or obliterated. This leads to a very quickly developing ascites, presumably because the portal blood coming from the intestines is more toxic and harmful to the lining endothelium of the vessels than is the systemic blood in general. With extreme congestion there may be multiple capillary hemorrhages. Lastly, malnutrition is apt to affect the tissue cells also, and these may show evidence of degeneration.

Stasis.—Slowing of the blood stream may become so extreme that its onflow is completely arrested, and there is brought about a condition of stasis. The capillaries of a part are found intensely distended, as also the veins (if this condition is caused by venous obstruction); the arteries also are distended, as a result of the obstruction in front. As a

consequence of the malnutrition and dilatation of the vascular walls the fluid of the blood tends to escape into the surrounding tissues, and the more concentrated corpuscles become so compressed as often to appear as a homogeneous hyaline mass. This **conglutination** must not be mistaken for coagulation; with removal of the obstruction and resumption of circulation the individual corpuscles may again become loosened one from the other. Prior to this stage of conglutination, the weakening of the distended capillary walls may result either in escape of some of the erythrocytes into the surrounding tissues, either through spaces in the walls (hemorrhage **per diapedesin,** see p. 437), or as a result of actual rupture (**per rhexin**).

The causes of such stasis may be either (1) obliteration of the efferent vein of the part; (2) obliteration of the afferent artery, with regurgitation of blood from surrounding capillaries into an area which now has no stream through it, but has become a "backwater" (see **red infarct,** p. 423); (3) chemical and physical agencies acting directly upon the capillaries of a part, *e. g.,* heat, caustic agents, toxins, and other bodies inducing acute inflammation.

Local Anemia.—Local anemia may (1) be part of a **general** bloodlessness, as after profound hemorrhage, or may be (2) **collateral** or compensatory, as where the determination of blood to one region leads to inadequate blood supply to others, as is well seen in the cerebral anemia of syncope (p. 183), or may be (3) due to local disturbance, as in the spastic contraction of the artery or arteries of supply of a region (**neurotonic anemia**) seen in **Raynaud's disease (symmetrical gangrene),** and in the superficial tissues under the action of cold, or again through the direct agency of adrenin and other vasoconstrictor drugs; may be caused (4) by obstruction to the arterial inflow to a part as (*a*) by pressure on that artery from without by new growths, ligation, etc., (*b*) by disease of the arterial walls, (*c*) obstruction to its lumen either by foreign bodies, as in embolism (p. 434), or by intravital coagulation of the contained blood (thrombosis, p. 428), (*d*) section of the vessel, etc.; may be caused (5) by direct compression exerted upon a part (Esmarch's bandages, pressure of aneurysms, and other tumors upon the surrounding tissues). Pressure is, however, more apt, save when extreme, to tell first upon the less rigid veins, and as a result, passive congestion rather than anemia is the more frequent. It will be recalled that if a pressure less strong than that required to arrest the pulse below, is applied around the proximal part of a limb, the result is a well-marked passive congestion and swelling of that limb, and thus an incarcerated hernia presents a similar venous hyperemia and not anemia.

Results of Local Anemia.—These are primarily (1) pallor, (2) some reduction in size due to lessened filling of the vessels, (3) firmer consistency, (4) lowered temperature, (5) arrested function. With these there may be subjective symptoms—numbness, "pins and needles," agonizing cramps, and sometimes intense pain. The after-effects may be very serious unless conditions favor the development of a collateral circulation. These results we will consider in some detail.

Closure of Vessels and its Effects.—Arterial Occlusion.—The results of closure of an artery are influenced by many factors: (1) the rate of closure, whether sudden or gradual; (2) the existence of anastomosing arteries; (3) the relative size of these collateral vessels; (4) the extent of

FIG. 220
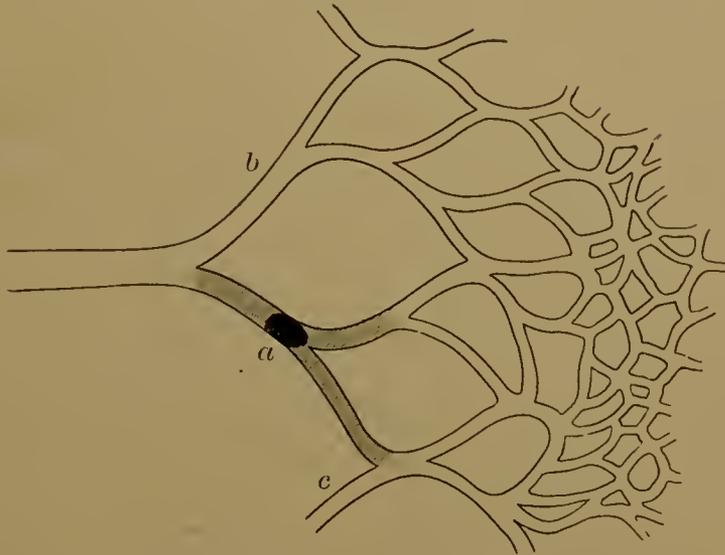
Schema of an anastomosing circulation. If a branch be ligatured or blocked as at *a*, the region supplied by that branch receives abundant blood through the anastomoses between it and other arteries, *b* and *c*. At most there is an arrested circulation in the artery itself as far as the nearest points of branching or anastomosis above and below.

FIG. 221
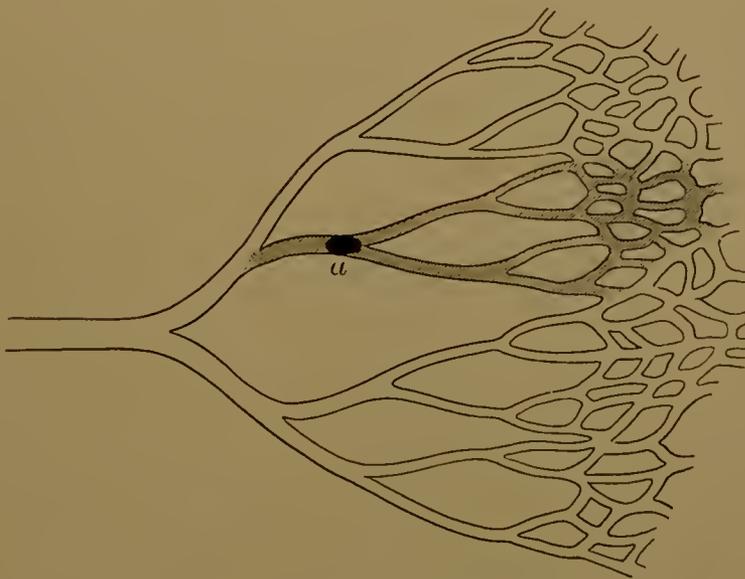
Schema of a terminal arterial system in which the anastomoses are only between the capillary loops. It will be seen that a ligature or obstruction at the point *a* may cut off the whole blood supply of the region supplied by the obstructed artery and its branches, unless the capillary circulation provided by neighboring arteries be so abundant as to afford nourishment to the blocked area.

the area supplied by the closed artery; (5) the arterial blood pressure; (6) the venous blood pressure; and (7) the difference between the two latter. Slow occlusion, for example, extending over days (as in the case of disease of the arterial wall) affords time for the development of an adequate collateral circulation. Such collateral circulation may be present, but the anastomosing vessels may be of insignificant size, and

sudden occlusion in these cases may lead to death of the tissues of an area before the collateral vessels undergo sufficient distension to carry the blood supply needed for the part. A good example of this is seen in connection with the heart. Anastomoses exist between the different branches of the coronary artery; but these are small, and as a result a sudden blockage of one branch is followed by death of its area of supply (infarct formation).

FIG. 222
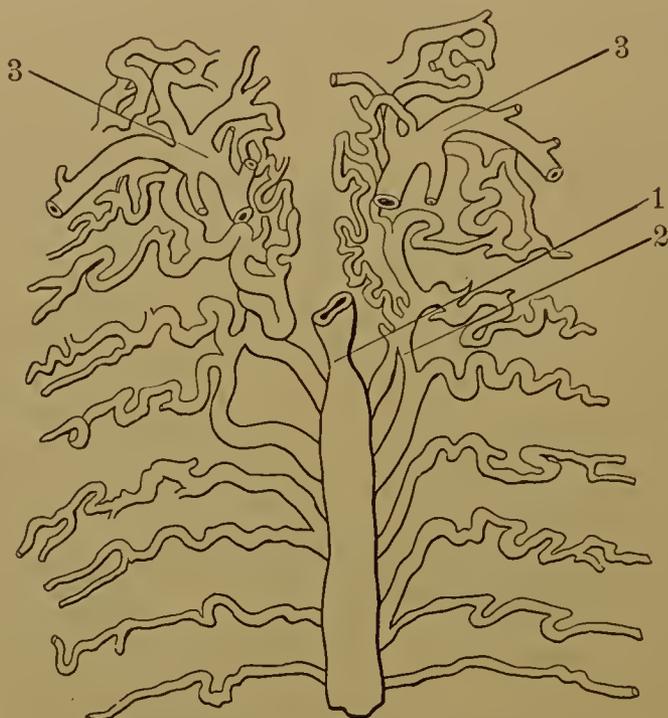
The main trunks of a collateral circulation established by means of the intercostals and neck vessels between the arch of the aorta and the dorsal aorta in a case of coarctation or congenital obstruction of the aorta in the region of the ductus Botalli. 1, region of coarctation; 2, anastomotic branches between the intercostal arteries; 3, subclavian arteries. From a man, aged thirty-five years. (After J. F. Meckel and Thoma.)

This presence or absence of anastomosing arteries is of high importance. Cohnheim divided the arteries of the body into two orders, the *anastomosing* and the *terminal* or end-arteries. The accompanying diagrams indicate the nature of the two. Of the former the most striking example is the circle of Willis; the anastomosing arteries there are so considerable that obviously if one be blocked, blood can easily flow into its branches from the other contributory vessels. In the muscles also and the skin (save the very smallest superficial vessels) anastomoses are abundant; it requires the simultaneous blockage of several arteries to arrest the circulation. Of Cohnheim's terminal arteries the most marked instances are the *arteria centralis retinæ*, the renal artery and its branches, the splenic artery and its branches, the arteries within the brain, and the spermatic artery. These are held to possess no communication between their capillary areas and branches of other arteries of like or different origin. We are of opinion that this is purely a matter of degree. Careful study of the kidney, for example, reveals occasional anastomoses between branches of the cortical arteries, and experimentally it can be shown that underlying the capsule the

capillary area is common to the capsular and the cortical arteries. In the heart muscle also, as already noted, clear arterial anastomoses exist, but despite their existence, identical infarct production occurs when a coronary artery or one of its main branches is blocked, as when the arteria centralis retinæ becomes obliterated. The same considerations apply to the intestinal arteries; anastomoses occur between the superior mesenteric and the many *rami duodenales* of the pancreatico-duodenal artery above and the *rami colici* of the inferior mesenteric below, as again between the successive branches of the superior mesenteric. If a small branch of this last be blocked the anastomoses may be adequate to prevent any arrest of the circulation; if a larger, gangrene of the intestines inevitably supervenes because these anastomoses are inadequate. *It is not the existence or non-existence of anastomoses that should trouble us, but the presence or absence of adequate anastomoses;* if the surrounding arteries, whether directly or indirectly through their capillaries, cannot rapidly afford adequate blood to preserve the vitality of the area whose direct supply has been arrested, then death of that area must follow, resulting in a **focal necrosis**, when only a small capillary area is involved, in an **infarct** where the area of distribution of an arterial branch is involved, and **gangrene** or **mortification** where one of the larger arteries supplying a part is, with its branches, cut off from the circulation. These three terms indicate grades of extent of disturbance rather than different processes.

Development of Collateral Circulation.—Where a large artery, such as the femoral becomes suddenly obliterated, the limb becomes numb, cold, and paretic. Slowly during the course of days it regains its temperature and muscular power. We know from dissection that anastomoses exist between the femoral and its branches and the other arteries of the lower limb, but obviously at first these cannot supply sufficient blood to the part. The returning warmth shows that gradually these enlarge until the collateral circulation becomes complete. The gradual enlargement of collateral vessels occurs to quite a remarkable degree; and it has been determined experimentally that even capillary channels in this process of distension may become arterial, gaining the structure of arteries.

Venous anastomoses are freer and more widespread than are arterial; as a result the extent of the collateral circulation set up is at times very extraordinary. When, for example, the portal vein becomes obstructed, the blood from the abdominal area may find its way to the heart through the coronary veins of the stomach, and so to the œsophageal veins; through those of the gastro-epiploic omentum to the diaphragm and so to the *vena azygos;* through anastomoses between the inferior mesenteric and the hemorrhoidal veins; through the veins of the round and suspensory ligaments of the liver to the epigastric and mammary veins and so on.

Infarct Formation and Mortification.—Where, as above noted, the anastomoses are inadequate to restore the circulation before the tissues die

(and here it must be noted that tissues vary in their vitality so that, for example, glandular organs are more sensitive to nutritional changes than are muscle and connective tissues), then a characteristic series of changes manifests itself. Of these, paradoxically, the first is a swelling of the affected area so characteristic as to afford the name given by Virchow, of **infarction** or "stuffing." This swelling is due to great distension of the capillaries with blood. They become intensely congested, and at the same time the tissue cells of the part show a series of changes ending in failure of their nuclei to stain and complete death.

How does this congestion come about? Cohnheim held that as with blocking of the artery of supply, the blood pressure beyond the block is reduced to nil, and as the surrounding veins have a positive pressure the blood falls, as it were, from them into the area until the pressure there reaches that in the surrounding capillaries. The matter, however, is not quite so simple. It has been shown that in the kidney, for example, the congestion becomes even more extreme when both the artery and the vein are ligatured, also that after the artery has been ligatured blood continues to be discharged from the vein. Evidently, therefore, the collateral arterial supply of this organ through the capsular vessels, and through the pelvis from the ureteral, is more extensive than we are apt to imagine. Wherefore it would appear that after ligation of the artery going to a part the pressure communicated to the capillary circulation through these collateral arteries is sufficient to distend the capillaries of the affected area, although insufficient to drive the capillary blood forward, or to supply adequate nutrition. This imperfect aëration in itself is a factor in the loss of tone and dilatation of the capillaries.

Experiments by Greenfield, of Edinburgh, and his pupils, confirming earlier studies of Vulpian and Hardy, demonstrate that in its first stage —within five hours of the obstruction—an infarct is always intensely congested, reddish-purple, and raised. Later, if not too large, as both the cells of the part and the blood corpuscles undergo necrotic changes, the hemoglobin becomes diffused out, and the part becomes paler and of a more pinkish color. It is in the early part of this second period that the infarct shows best the condition termed **coagulation-necrosis**. The cells no longer stain; they become hyaline or very finely granular shadows of themselves. At first the individual cell outlines are still distinguishable; soon tissue cells, capillaries, and their contents become fused into a firm homogeneous or almost homogeneous hyaline mass.

In this way the **hemorrhagic or red** infarct and the "**anemic**" or "**white**" infarct may be regarded as two stages in the one process. But here certain complications enter: (1) the hemoglobin may not diffuse out of the centre of a large infarctous area so that there may be complete hemorrhagic necrosis without pallor, and (2) in certain tissues (lung, liver) the infarct does not proceed beyond the red stage, and that because, owing to the existence of a double blood supply, the coagulation necrosis stage is not reached. Thus, if a branch of the pulmonary artery becomes occluded, the result is intense congestion of the region of supply, congestion so intense that the corpuscles escape into

and fill the alvcoli; but sufficient blood still reaches the alveolar walls through branches of the bronchial arteries to maintain their vitality. Similarly, if a branch of the portal vein be occluded, a like red infarct is produced, but the liver cells do not undergo necrosis, gaining sufficient nourishment through the branches of the hepatic artery.

It follows thus that the red or hemorrhagic infarct is of at least three orders; and a fourth may here be noted, namely, that the local death of tissue accompanied by intense congestion and all the features of infarct formation may equally be brought about by *occlusion of the efferent vein of the part,* provided that there be no adequate anastomoses. While, for example, the majority of red infarcts in the lung appear to be due to blocking of a branch of the pulmonary artery, in a certain number of cases a like condition is produced by intravital coagulation of the blood in a branch of the pulmonary vein. It can easily be imagined how in these cases, owing to lack of exit, there is most intense congestion of, with hemorrhage from, the capillaries of the affected part, and how the stasis is liable to be followed by tissue death. This venous form is always of the hemorrhagic type. An organ in which it is apt to occur is the adrenal, and this particularly in young children, in them being a cause of relatively sudden death. The whole organ is found intensely hemorrhagic.

It deserves note that arteries of the terminal type most frequently exhibit a dichotomous branching and spread thus from the hilus of an organ in a fan-like manner toward the periphery. The typical infarct, therefore, is wedge-shaped, with the apex directed toward the hilus, and the base beneath the surface of the organ. We say *beneath,* because usually the infarct does not come absolutely to the surface. In general, a superficial layer is to be made out of tissue that is congested but not necrosed, tissue that is prevented from necrosis by the collateral circulation established in it, through the capsular vessels.

Results of Infarction. — 1. **Complete Resolution.**—Complete resolution may occur where the infarction is imperfect and, as in the lung, does not result in complete necrosis. Capillary infarcts and focal necroses may also be followed by no obvious results, the destroyed tissue cells being replaced by regeneration after leukocytes have migrated into the part, and have aided in the digestion and removal of the necrosed tissue and fibrin.

2. **Organization and Cicatrization.**—These are the typical events in the ordinary infarct. Very rapidly the necrosed wedge of tissue is found surrounded by a zone of pronounced congestion, with leukocytic migration into the necrosed area, and at the periphery there may be a certain amount of regeneration of the tissue cells proper. In the more central area the dead tissue is removed by the agency of the leukocytes and tissue ferments, and now gradually the central dead area becomes the seat of a progressive formation of granulation tissue; new capillaries pass in from the surrounding vessels and become clothed with fibroblasts until a new connective tissue completely replaces the dead tissue, and then, after the nature of new connective tissue, undergoes pronounced

contraction, so that the end result is the production of a dense, depressed scar of firm connective tissue. Not infrequently we meet with these depressed cicatrices of old infarcts in the kidney and the spleen.

3. **Cyst Formation.**—Where there is little reaction on the part of the surrounding connective tissue, autolytic changes result in the necrotic tissue becoming eventually replaced by a serous fluid, encapsulated within a relatively thin layer of connective tissue. Such cyst formation subsequent to old infarction is most frequently met with in the brain (see p. 413).

4. **Suppuration.**—Suppuration may occur in small infarcts where the block has been due to infected material in the blood stream. As the microörganisms multiply and toxins diffuse, leukocytes may be attracted to the area in such abundance that a true abscess replaces the infarct.

5. **Putrefaction.**—Where the infarct is larger and becomes infected, the determination of leukocytes to the part may be inadequate, and with the growth of the bacteria the cells are broken down and liquefied, an area of putrefaction rather than of true abscess formation being the result.

6. **Calcification.**—Rarely calcareous salts may be deposited in the infarcted area.

Mortification or Gangrene.—We have already noted that where limbs or large areas are involved in this process we speak of mortification rather than of infarct formation. In these cases saprophytic organisms from the surface are apt to grow into and invade the dead tissue, leading to extensive putrefaction. We have already described the stages and forms of this mortification or gangrene (see p. 298).

Thrombosis.—The main cause of infarct formation and local arrest of the circulation is *embolism*. But, as dislodged particles of thrombi are the most frequent causes of embolism, it will be better to discuss first the subject of thrombosis.

Thrombosis is the intravital deposit of constituents of the blood in a solid form within the vessels. It is a process frequently found at post mortems. Here we must distinguish between post mortem clotting and intravital, and at times this is difficult. The following are the main features: (1) blood that has clotted in vessels after death (**cruor**) has done so by a process identical with that which occurs in blood removed from the body. It is a true coagulation, with fibrin formation. (2) It shows no stratification; the blood has coagulated *en masse*, save that just as with blood coagulated slowly outside the body, the lighter leukocytes may rise to the top and form a "buffy coat," so sometimes we find this post mortem clot red throughout, at other times, notably in the auricles of the heart, we find a superficial and upper pale layer and a lower mass of red clot, the significance of upper and lower being determined by gravity. Where there is a condition of marked leukocytosis, this pale layer is extensive, with a yellowish tint and translucency, earning for it the title of "**chicken-fat**" clot. (3) Under the microscope this postmortem clot presents the same appearance of a network of fibrin, inclosing corpuscles, which is seen in extravascular blood clot. (4) It is moister and less friable than is an antemortem thrombus.

(5) It is not adherent, but, on the contrary, is easily removed from the cavity in which it lies.

The thrombus, on the contrary, is firmly adherent at some point, or, if not adherent, search will show a detached surface and a region in the vessel or cavity where it had previously been attached. It is dry and more friable; seen under the microscope the arrangement of its constituents is different from that seen in an extravascular clot.

The conditions, in short, leading to coagulation and thrombosis are different. According to modern teaching, coagulation is essentially brought about by the formation of fibrin as a fine network. It is here necessary only to recall that this formation is due to the action of fibrin ferment or **thrombin** upon certain of the proteins present in the blood plasma. This ferment is not present in the normal circulating blood, but is produced after the blood is discharged from the vessels by the action of a **thrombokinase** upon the **thrombogen** of the plasma in the presence of calcium salts. The thrombokinase in its turn is supposed to be liberated in the breaking down of leukocytes and blood platelets, although tissue cells also may afford a **coaguline** which activates the thrombogen. Opposed to this thrombokinase, there exist, according to Brücke, substances which hinder coagulation, given off, more particularly, by the endothelial cells of the vascular intima.

The characteristic of the **thrombus** is that the fine network of fibrin is not an essential. Perhaps the best idea of the nature of thrombosis is gained from a study of the successive stages of its experimental production. It is well known that if a foreign body be introduced into the blood stream a clot or thrombus tends to form around it. We owe to Eberth and Schimmelbusch the first clear studies upon what occurs in this process. They introduced a fine needle point through the vessel wall, and observed a very striking process; namely, they found that the first step is the accumulation upon the foreign body of *blood platelets*. What these blood platelets are has been subject of debate, but this is certain that they are present in varying numbers in normal blood, and that a reduction in their number characterizes conditions in which there is delayed or imperfect coagulation of the blood (**hypinosis**). The studies of J. H. Wright have demonstrated positively that some of them, at least, originate in the bone marrow by the breaking off of processes from the megacaryocytes of that tissue. Arnold and others hold that some, at least, originate from red corpuscles. Accumulated thus the blood platelets run together or undergo conglutination into a homogeneous or finely granular mass, and not into fibrils, and with successive deposit of more blood platelets the vessel lumen may become filled with (1) a pure hyaline blood platelet thrombus. Often, however, the leukocytes of the circulating blood also become adherent to the mass when we speak of (2) a mixed blood platelet and leukocyte thrombus. Or, under certain conditions, more particularly where there is pronounced stasis of the blood, a thrombus beginning thus passes on to the condition akin to coagulation proper, and coarse hyaline bands

and processes of conglutinated material enclose in their meshes the red corpuscles, so that (3) a mixed red thrombus is produced.

These are the main types, but also in the smaller vessels we occasionally encounter (4) hyaline thrombi, which it is difficult to explain other than as due to a conglutination or agglutination, not of blood platelets, but of red corpuscles, as may be seen in inflammatory stasis (see Fig. 25).

Factors Favoring Thrombosis.—1. **Loss of the Integrity of the Vascular Endothelium.**—This is a factor of the first order. Baumgarten and Lister have shown that the blood may be kept fluid for days when enclosed in a vein between two ligatures, or in a "living test-tube," composed of a vein, ligatured before removal from the body, and then opened at one end, provided that in ligation the endothelium has not been damaged. On the other hand, the destruction of the endothelium, whether experimentally or by disease, is followed by thrombosis.

2. **Slowing of the Blood Current and Stagnation.**—Large thrombi occur in areas like aneurysms, where the blood stream is slowed; where, as in arteries, the stream is rapid, there may be little or no thrombosis. Thus thrombosis is much more common in the venous than in the arterial system.

3. **Eddying of the Blood.**—Von Recklinghausen held that this rather than simple stagnation explains the frequent origin of thrombi in the pockets of the valves of the veins. The centre of an eddy may be recalled as relatively stagnant, and the more peripheral whirl brings successive cells or blood platelets into approximation with the surface of the developing thrombus.

4. **Hemolysis.**—Agents leading to corpuscular disintegration favor extensive thrombosis. Such agents favor more rapid coagulation (or **hyperinosis**). Among them we may mention burns and freezing of parts, transfusion of blood from another individual or species, and various poisons, snake venom, foreign enzymes, ricin, toluylene-diamin, extracts of amanita and other poisonous mushrooms, and the products of cell degeneration. Of the same order may be cited the toxins of infections. Thrombosis, for example, is not uncommon as a complication of typhoid and other infectious conditions. In some of these cases we deal with a bacteriemia and find (as in acute endocarditis) that there has been a primary injury to the vascular endothelium. Such thrombi in themselves contain abundant bacteria. In other cases, however, the thrombi yield no bacterial growth, and in these we must suppose that the circulating toxins are the important factor both in injuring the vascular endothelium and in bringing about an increased coagulation power of the blood, this hyperinosis and the liability to thrombus formation appearing to proceed hand in hand.

Forms.—Thrombosis may occur in any part of the circulation proper. (*a*) **Cardiac** thrombi are frequent; the sites of election here are in the auricular appendices, and in the ventricles, originating either at the apices or in the pouches between the muscle bundles. All these are areas of relative stagnation of the blood, and, it may be added, of poor nutrition of the cardiac endothelium. Originating thus they

tend to form sessile, more or less globular masses, and, under the action of the blood current, often present a ribbed or coarsely netted surface. They are of some little duration. After a time these thrombi present a comparatively thin surface layer, enclosing a turbid fluid, the centre of the mass having undergone liquefaction through autolysis or leukocytic heterolysis. More rarely such a globular thrombus, originating in one of the auricular appendices, becomes pedunculate with progressive growth, and, being broken off, forms a **ball** thrombus. Free

Fig. 223
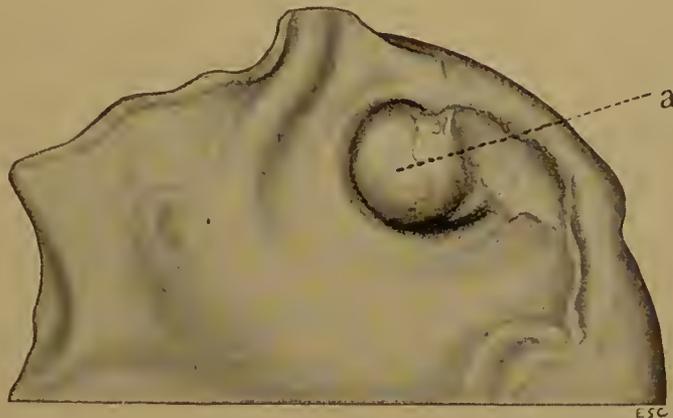
Globular thrombus of auricular appendix: *a*, globular thrombus filling and protruding from the auricular appendix.

Fig. 224
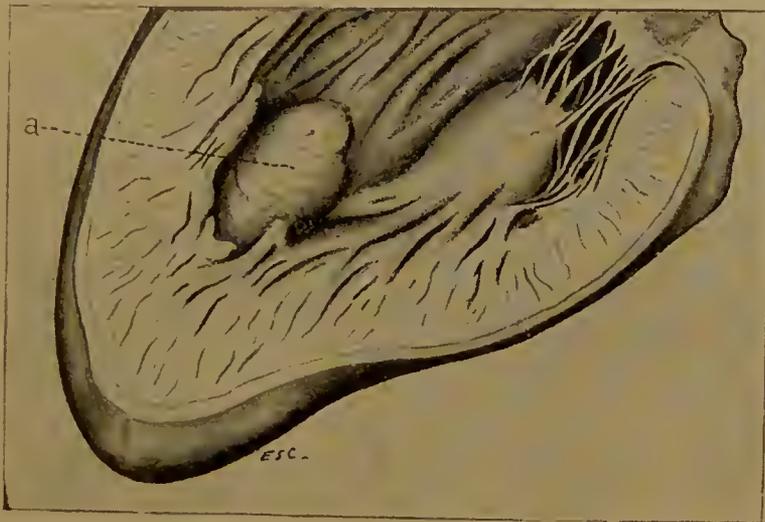
Globular thrombus of apex of left ventricle.

in the auricular cavity, such ball thrombi have been found to be a cause of sudden death, acting like a ball valve and occluding a narrowed mitral orifice.

Yet another form of cardiac thrombosis is of first importance. Those above mentioned are encountered in cases of obstructed circulation and slowed blood flow, whether through weakening of the cardiac muscle or through valvular disease. They are generally regarded as bland and non-infective. The other form is that found in acute (bacterial) endo-

carditis, in the form of **vegetations**, most often developing upon the cusps of one or other heart valve, but occasionally also growing as parietal thrombi upon the walls of ventricle or auricle. Such vegetations may be in the form of individual processes or outgrowths, or, at times, may develop into large cauliflower-like masses, adherent to the valves.

FIG. 225

Acute red thrombus of iliac vein
(McGill Medical Museum.)

From their consistency, and from the motion of the blood current, as also from the softening they may undergo through the action of the bacterial ferments, vegetations of this nature are peculiarly liable to become broken off and be carried forward in the blood stream.

As already noted (b) **arterial** thrombi are not so frequent as are venous. Nevertheless, they may develop both in the pulmonary artery and in the aorta or its branches. More frequently they are parietal, growing from some diseased area of the arterial wall, and at times they may completely fill the vessel, forming an occluding thrombus. It is interesting to note that it is exceptional for such arterial thrombi growing downward to extend into the capillaries. When (c) **capillary** thrombosis occurs it is due to direct local irritation or disease.

(d) **Venous** thrombi are relatively common, occurring in the pulmonary, the systemic, and the portal circulation. The slower flow of the blood, its poorer quality, the presence of the valves, the low blood pressure, and easy compressibility all favor thrombosis, and once the process has begun in a vein, it is apt to extend in both directions, so that, for example, a thrombus originating in the femoral vein, may extend up into the iliac veins and involve all the branches of the femoral below, while a thrombus forming in the veins of the uterus may progress until it fills the internal iliacs of either side.

The Results of Thrombosis.—An obliterating thrombus of a vessel produces those conditions of arrested circulation, in the area of supply or origin, that have already been discussed. If the thrombus, or part of it, becomes loosened and carried along the blood stream, its effects are those which we shall discuss in our next section when treating of embolism.

As to the changes that may occur in the thrombus itself, the following may be said:

Once laid down, the fibrinoid framework of the thrombus tends to contract and drive out the excess of plasma, hence the thrombus becomes relatively dry. If the thrombus is small, the indications are that, through the agency of leukocytes, it may (1) undergo complete **absorption** and removal, with restoration of the circulation to the part, or (2) it may undergo **organization**. We have already pointed out that at the region of attachment of the thrombus the lining endothelium of a vessel is destroyed. It is at this point that the

Fig. 226
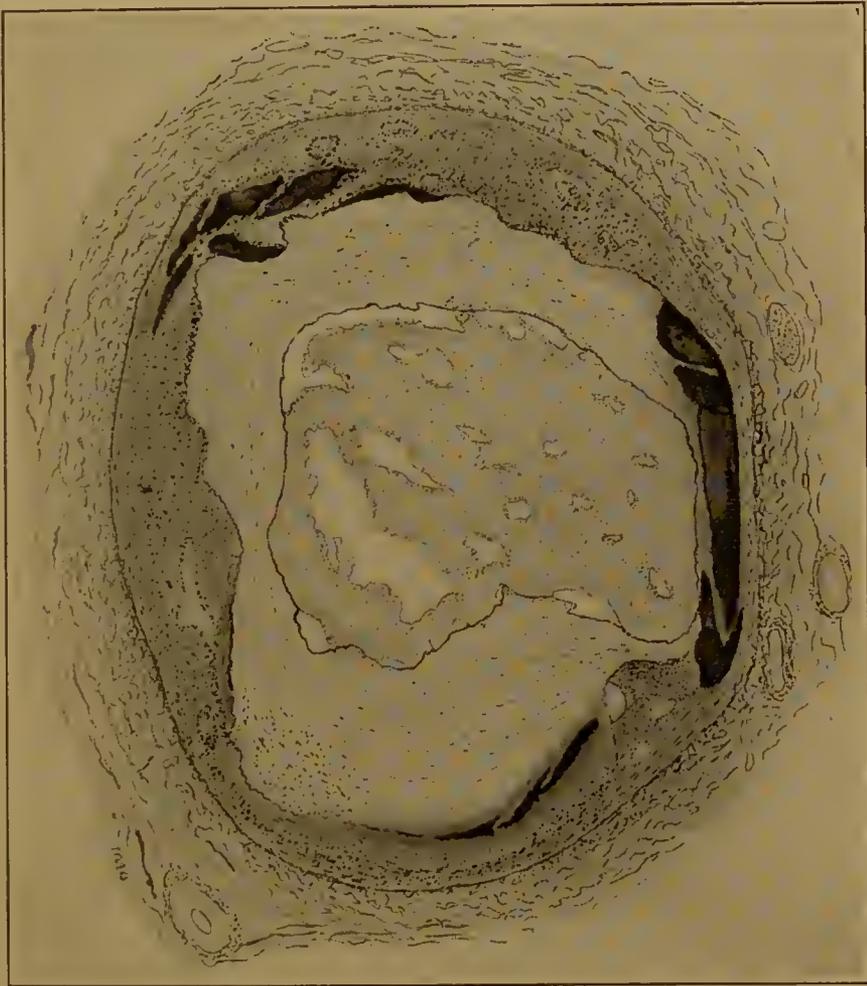
Tibial artery, sclerosed, with organized and canalized thrombi. The clear spaces represent what is now the lumen of the vessel. From a case of senile gangrene of the foot. (Prof. Oskar Klotz.)

thrombus acting both as a foreign body and irritant, leukocytes make their way into it from the vasa vasorum, and following upon these there is a passage in of capillary loops and processes. In this way, just as in ordinary granulation tissue, first there is a solution and progressive removal of the thrombotic material, and this is followed by the laying down of fibroblasts and new connective tissue. The thrombus thus eventually becomes represented by a shrunken mass of dense connective tissue. The network of new capillaries, in

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this newly forming tissue, may open above and below into the lumen of the vessel, and so not infrequently we find the development of **canalization**, one or several channels of fair size restoring the continuity of the vessel. At times indeed the only indication of an old thrombosis is the presence of fibrous bridges stretching across a vessel.

(3) **Autolysis**, as we have already noted, is liable to occur in old cardiac thrombi.

(4) **Putrefactive Softening.**—This also has already been referred to, but two processes must be distinguished. There may be a simple puriform, but not truly purulent, softening of a thrombus. This, for example, is not infrequently seen in thrombosis of the lateral sinus and internal jugular vein following upon infective middle-ear disease. The thrombus is liquefied through bacterial agency, without any marked invasion by pus cells. Or, on the other hand, as we at times note after appendicitis, progressive thrombosis of an infective nature, involving the inferior mesenteric vein, may either be the result of an ascending infection of the wall of the vein, or may itself set up inflammation of the wall (**thrombophlebitis**). Where this is the case there may be an abundant migration of leukocytes into the thrombus, and softening, associated with true suppuration. (5) In certain regions of the body, where there are abundant venous anastomoses, as in the uterine and prostatic plexuses, we encounter **phleboliths**, somewhat elongated, oval bodies, lying loose in the lumen of a vein, which have undergone calcification. These are old bland thrombi, are characteristically unattached, and instead of being absorbed they become infiltrated with calcareous salts.

Embolism.—Any body which, carried along by the blood stream until with the narrowing of the lumen it becomes arrested and blocks the vessel, is known as an embolus, literally, something thrown in.

Forms of Embolism.—It is interesting to note how many diverse bodies, foreign to the normal blood, may thus constitute emboli.

Liberated Thrombus or Vegetation.—(1) Quite the commonest is a liberated thrombus or a cardiac vegetation. The former, liberated in the systemic veins, may either become arrested in the right heart, *e. g.*, the conus arteriosus, or, passing through the heart, in some branch of the pulmonary artery, or originating in the pulmonary veins or left heart, become arrested in some one of the arteries, or, lastly, originating in the portal system, is arrested in the liver. A detached venous thrombus is apt to be somewhat elongated, is apt further to be arrested at the point of bifurcation of a branch of the pulmonary artery. So, often, it forms what is known as "riding" embolus, riding over the angle of the bifurcation and extending down the two branches. It is apt to be continued down the two branches by a process of secondary thrombosis extending from the free ends.

2. **Calcareous and Atheromatous Emboli.**—Calcareous and atheromatous matter from atheromatous ulcers may also potentially form emboli, but these are not often encountered.

3. **Cell Emboli.**—Tumor masses and cells, originating from new growths which have penetrated the vessels, forming emboli, may continue to grow, and thus give origin to metastases. **Tissue cell** emboli also occur. Of these the more frequent are **placenta cell** emboli, derived from the fœtal villi, which have penetrated into the uterine sinuses, and **liver cell** emboli, the cells being liberated into the hepatic vein after some sharp and long compression upon the organ. These would seem to be more of the nature of pathological curiosities than causes of serious disturbance. Another cell which may also become liberated into the circulation is the giant cell or **megacaryocyte** of the bone marrow, which is apt to be liberated in the delicate capillaries in cases of pronounced leukocytosis. Very rarely osteoclasts and fat cells from the marrow have been detected in capillaries.

Of cells that naturally are present in the blood, the leukocytes, in cases of myeloid leukemia, may be so densely packed into the capillaries of various organs as to constitute emboli.

4. **Fat Embolism** follows upon extensive concussion of the bony skeleton, such as may be caused by a fall from a height. So, also, after fracture of the long bones, with rupture of the fat cells of the marrow, after forcible breaking down of stiff joints, operative handling of fatty tissues, such as the omentum and panniculus adiposus, numerous capillaries of the lung may be blocked by fat. Where only a few capillaries are involved, at most minute infarcts may be produced, with no serious results. There may be a small surrounding congestion and some migration of leukocytes; gradually the fat seems to become saponified and so removed. Its presence in great abundance may seriously obstruct the circulation through the lung, and may even produce a fatal dyspnœa. The emboli may become loosened from the lung capillaries, and passing through the left heart, have been encountered in the capillaries of the heart, kidney, and brain. A somewhat similar condition is at times met with in the lipemia of diabetes, but here no reaction is seen; apparently the fine fatty globules present in the blood have run together and creamed as a post mortem phenomenon.

Of emboli due to extraneous matter the following may be noted.

5. **Air Embolism.**—The negative pressure most marked in the veins nearest to the heart during inspiration, sometimes leads to air being sucked into one of these veins during the course of an operation, or after trauma. If the quantity so inspired be small, no results may ensue; if larger, death at times occurs with absolute suddenness; at times after a period of extreme dyspnœa, with cyanosis and convulsions. Cases are on record where sudden death, apparently due to this cause, has followed operation upon the head and upper extremities, and from entrance at the placental site during or after labor. There is still some debate as to the exact cause of death. Some cases are evidently cardiac, due to the expansion of the warmed air and its becoming churned into a froth in the heart, the froth impeding the action of the auriculoventricular valves. In other cases the formation of abundant capillary emboli in

the lungs or brain seems to be the lethal agent. Thus in these cases the lungs have shown multiple hemorrhages, indicating obstruction of a large number of capillaries, with congestion and rupture.

The dangers commonly attributed to the entrance of air into the circulation have not been entirely substantiated by experiment; on the contrary, large amounts of air have been injected, even under considerable pressure, into the jugular vein of the horse without serious effect.

6. **Gas Emboli.**—Rapid death may follow if proper precautions be not taken, when those who have been working under compressed air return to the ordinary pressure. There may be either pronounced dyspnœa and asphyxia, rapidly fatal, or a succession of nervous disturbances, which may be recovered from, or prove fatal after a few days. This **caisson disease** has been experimentally proved to be due to the increased solution of air in the blood under pressure. The oxygen of that air is utilized by the tissues, but the dissolved nitrogen is apt to be liberated from the blood in the form of gaseous bubbles, as gas bubbles form in a soda-water bottle just opened, and in the capillaries, notably those of the brain and spinal cord, these form emboli. The injection of peroxide of hydrogen into the cavities of the body has been followed by grave cerebral symptoms, apparently due to air embolism, and in a certain proportion of cases of infection by the Bacillus Welchii the production of gas in the vessels occurs ante mortem, so that gaseous embolism may be one of the causes leading to a fatal event.

7. **Bacterial Emboli.**—Although the statement has been made it seems scarcely rational to attribute to bacteria the power of directly blocking capillaries. Their presence in a capillary is the signal for a lesion of the wall, and thus the usual process of thrombosis is instituted.

8. **Pigment Emboli.**—These occur in the smaller capillaries of the brain, kidney, and other organs in malaria. These emboli are composed of the debris, pigmented, of the hemamœba of malaria left after the spores have been discharged.

9. **Parasitic Emboli.**—Closely allied is the accumulation of trypanosomes in the cerebral capillaries, which, according to some observers, is the main cause of the somnolence characteristic of sleeping sickness. Metazoan parasites, such as the abundant larvæ of various strongyles, may also induce embolism. After the rupture of an echinococcus cyst, some of the daughter cysts may find entrance into a vein and so lead to embolism of a pulmonary vessel.

10. **Foreign Bodies.**—Lastly, some three cases are on record in which bullets entering the heart or larger vessels have been carried along in the blood stream until they have become fixed in some smaller artery. We have ourselves seen a bullet lodged in the femoral artery after piercing the anterior wall of the dorsal aorta.

The Results of Embolism.—These have already been discussed when treating of the closure of arteries and infarct formation. To repeat, whether an infarct be formed or not depends upon the extent of the collateral circulation. As to the result upon the vessel itself, there may

be either organization and obliteration of the vessel; abscess formation where the embolus is infective; aneurysm formation through weakening of the arterial wall; formation of metastatic growths, etc.

Hemorrhage.—Hemorrhage, the act of escape of blood out of the vessels, and the results, local and general, of that escape, may be of two orders—that brought about by gross breaches in the continuity of the vessel wall, hemorrhage **per rhexin**, and that occurring in capillary vessels without breach of continuity, but through the insterstices of the wall, hemorrhage **per diapedesin**. (1) The former may be cardiac, arterial, or venous, and may be brought about by trauma, by disease and weakening of the vessel walls, and by grave alterations in the relations of the pressure acting upon the vessels from without, and the blood pressure within the vessels—whether by undue lowering of the external pressure, or undue raising of the blood pressure, or, lastly, by a combination of these causes, *i. e.*, an increase in blood pressure through sudden exertion which would have no effect upon healthy arteries may lead to cardiac or arterial hemorrhage in one suffering from disease of the myocardium or syphilitic disease of the aorta. Here may be noted a rare order of hemorrhage, regional, capillary, and apparently *per rhexin*, that, namely, of nervous origin, seen occasionally in hysterical individuals. The "stigmata" on the hands and feet of religious enthusiasts are of the same order.

(2) Hemorrhage *per diapedesin* occurs from the capillaries and venules as a result of active or passive congestion. It is generally held that the passage of the blood elements occurs between the endothelial cells by expansion of the bridges and spaces between those cells. Impoverished nutrition of that endothelium still further favors the escape of blood, as does lack of support by surrounding tissues. Consequently, this form of hemorrhage is particularly liable to occur where the capillaries are superficial, as beneath serous surfaces and in the lung alveoli. A similar oozing of blood may show itself where the arterial wall is thinned and its endothelium imperfect, as in false aneurysms.

Various names have been given to hemorrhages in different regions; thus a **cerebral apoplexy** is a hemorrhage brought about by rupture of one of the arteries of the base of the brain, and its results; **hematemesis**, a gastric hemorrhage, or, more accurately, its results, the escape of blood from the stomach through the mouth; **melena**, the discharge of blood per anum rendered black (μέλας, f. μέλαινα) by the action of the intestinal juices; **hemoptysis**, the expectoration of blood after pulmonary hemorrhage; **hematuria**, hemorrhage along the urinary tract causing bloody urine; **metrorrhagia**, hemorrhage into and from the uterine cavity at times other than the menstrual period; **menorrhagia**, excessive loss of blood at that period (μήν, a month); **hematidrosis**, bloody sweat. The terms **hematopericardium**, **hematothorax** explain themselves; a **hematocele** is the accumulation of blood in any body cavity (κήλη, a tumor). A **hematoma** is a localized projecting, tumor-like accumulation of blood in the tissues; **petechiæ** are punctate capillary hemorrhages; more diffuse capillary hemorrhages so close set that

they tend to run together are **ecchymoses** or **suggillations**; where these hemorrhages are multiple and subcutaneous we speak of **purpura**.

General Effects.—The gravity of a hemorrhage depends upon (1) the amount of blood lost from the vessels, (2) the rate at which it is lost (that amount which, withdrawn suddenly, leads to death may be lost several times over in recurrent smaller hemorrhages), (3) the region of hemorrhage (thus a hemorrhage of but an ounce into the brain substance, by pressure upon and obstruction of important centres and tracts may cause rapid death, where a pint withdrawn from the vein of an arm may be followed by a feeling of relative well-being). It may be laid down that the normal adult individual may suffer the loss of twenty ounces of blood without harmful effects, and of less than half the total volume of blood without necessarily fatal results; women bear the loss of large amounts of blood better than do men.

Taking these into consideration the general effects of hemorrhage may be:

1. Sudden death within a minute or two, as after rupture of the heart, or bursting of a thoracic aneurysm into the pleural cavity, pericardium, œsophagus, or trachea.

2. Death, preceded by collapse and all the symptoms of grave cerebral anemia.

3. Collapse followed by hydremia and eventual recovery.

4. Syncope or temporary cerebral anemia with rapid recovery.

5. No disturbances due to cerebral anemia, but, in cases of hemorrhagic extravasation into the tissues or cavities of the body, the development of a febrile state due to diffusion of the products of disintegration of the extravasated blood.

The above need little comment, save, perhaps, to note that diminution of the circulating blood below the normal amount is followed by a passage of fluid from the tissues into the blood vessels so as to restore in a few minutes the amount of fluid within the vessels; this passage renders the blood hydremic. So, also, secondary to any considerable loss of blood there is increased activity of the hematopoietic tissues, and notably an increase in the red marrow of the bones (increased production of erythrocytes). With repeated hemorrhages the marrow may become exhausted and the reproduction of red corpuscles be imperfect. Thus in a case of vascular papilloma of the bladder with hematuria extending over many months, we have seen developed a condition closely resembling pernicious anemia in every respect, save in a lack of increased iron content in the liver.

Local Effects.—The loss of continuity of an artery by deflecting the blood stream may lead to at least temporary lack of nutrition of the area of supply. In general, where there has been rupture there follows a natural process whereby the escape of blood is brought to an end: (1) where the escape is at all considerable the blood pressure becomes progressively lowered, and with this the rate of escape is lessened. (2) As the blood escapes through the wounded vessel into the tissues, contact

with those tissues, and their coagulins, induces coagulation, and this in its turn has a hemostatic action which becomes more complete the slower the blood stream. (3) The solution of continuity of the vessel wall, if the rupture be transverse, is followed by contraction of the middle coat, and diminution of the vascular lumen. If it be longitudinal, on the contrary, the contraction results in the opening remaining patent. But in general, besides (1) the direction of the rupture, the natural arrest of hemorrhage depends upon these main factors, (2) the size and nature of the vessel involved, whether artery, vein, or capillary, (3) the force of the heart action and blood pressure, and (4) the state of the blood, whether hyperinotic or hypinotic. There are those in whom a trifling contusion with rupture of vessels of inconsiderable size is followed by intractable hemorrhage endangering life, in whom, for example, the extraction of a tooth is dangerous. To these victims of **hemophilia** we have already referred, pointing out the hereditary nature of the diathesis (see p. 49). As to what is the exact nature of the state we are still in ignorance, whether there is an excessive development of antithrombin or a lack of kinase or coagulins. It has, however, been noted that the intravenous exhibition of horse or other blood serum tends to arrest hemorrhage in these individuals.

Next as to the fate of the extravasated blood. This, when it escapes into the tissues, undergoes coagulation; when it escapes into cavities lined by endothelium it may remain fluid for some little time, and in this fluid state may undergo reabsorption through the lymphatics both as regards its fluid and its corpuscles.

In petechiæ and minute hemorrhages into the tissues, through the agency of leukocytes the extravasated corpuscles after undergoing disintegration may be completely absorbed, although often some pigment is left behind, leading to a coloration which disappears in the course of weeks and months.

Where the hemorrhage is more extensive the following changes may occur:

1. Escape of hemoglobin from the extravasated erythrocytes with hemoglobin **imbibition** and discoloration of the area.

2. Disintegration of the escaped hemoglobin with production of **hemosiderin** and **hematoidin** (see p. 289). The different stages in the disintegration lead to a series of color changes (as seen in the familiar "black eye").

3. Absorption of the pigment and disintegration products by leukocytes, which may be found in the area, containing pigment and other granules.

4. Where the hemorrhage is large and the absorption incomplete there may, as in some hematomas, be a production of surrounding granulation tissue and eventual production of a **hemorrhagic cyst** (p. 413), the contents of the cyst becoming eventually a colorless serum.

The bactericidal powers of the blood are such that it is rare for a hemorrhagic extravasation to become infected and terminate in abscess formation or putrefaction.

QUALITATIVE CHANGES IN THE BLOOD

In this section we have to pass rapidly in review the main data concerning the variations in the plasma and the corpuscular elements of the blood and their relationship to disease.

The Plasma.—We are but at a beginning of our knowledge concerning the significance of changes in the composition of the plasma. While it is relatively easy to determine the variations in its main elements, water, serum albumin and serum globulin and salts, we are coming to realize that constituents present in quantities too minute to be isolated by chemical methods exercise a profound influence upon the body at large— enzymes, hormones, toxins, and antitoxins. Biological as well as chemical methods have to be invoked in order to gain a completer knowledge of this great medium of interchange between the various tissues, this stream which is at once the nutritive medium and the sewer of the body.

As regards its main elements, what impresses us is the evidence of the existence of mechanisms which in the normal state keep their ratio extraordinarily constant, so constant that, as A. B. Macallum has pointed out, the salts still retain the relative proportion characteristic of that ancestral period when, with free communication between the body cavity and the external medium, the internal tissues were bathed in but slightly modified sea-water. Nevertheless, in disease variations are manifest. Thus, as already indicated, a condition of **hydremia** is not infrequent, of increase in the plasma relative to the corpuscular elements, with accompanying lower specific gravity. This may be brought about (1) by actual increase in the amount of circulating fluid, as in obstructive heart disease, (2) by no increase, but, on the contrary, decrease in the total amount of circulating fluid, as after severe hemorrhage, when with loss of blood the plasma undergoes a compensatory dilution, tending to maintain its volume. A similar relative hydremia is characteristic of conditions of grave anemia brought about, not by hemorrhage, but by intravascular death and disintegration of the erythrocytes, (3) by increase in the salts of the blood tending to attract more fluid, so that the hypertonic state of the plasma may be reduced to the normal. This process has been invoked to explain the hydremia of nephritis, in which there are evidences of increased retention of chlorides in the system, though here also the loss of the proteins of the blood by escape into the urine may be a factor of some importance. Thus, briefly, a hydremic state of the blood may be encountered (1) in obstructive heart and lung disease, (2) in kidney disease, more particularly the acute parenchymatous form, (3) after severe hemorrhages, (4) in conditions associated with destruction of the red corpuscles, severe infections, advanced malignancy, and pernicious anemia.

Of the proteins of the plasma (as contrasted with blood serum) we have already called attention to the conditions of **hyperinosis** and **hypinosis,** due presumably to differences in the ratio between fibrin-

ogen and fibrin ferment. But in the generality of cases it would appear that we have to deal not so much with an excess or deficiency of the substratum to be acted upon, the fibrinogen, as of the kinase and its concomitants, the calcium salts, etc. It is the rate of coagulation rather than the amount of fibrin that shows the greatest variation. There are, however, indications that in certain conditions the amount of fibrinogen, and so of fibrin produced, is definitely below the normal.

Of the salts of the plasma (sodium salts, chlorides, phosphates) this may be said, that they play a part in the solution of the proteins and are normally present in such relationships that the plasma is definitely alkaline. Reduction of the alkalinity (**acidosis,** p. 100) is followed by the gravest metabolic disturbances.

Lipemia.—From the normal plasma there can always be isolated a minute quantity of fat, but occasionally we meet with an extraordinary increase in this fat, a condition of lipemia. As in milk it is present in fine globules in the form of an emulsion. The amount may be such that the serum assumes a distinctly milky appearance. We know little regarding the causes leading to the condition, save that it is encountered in diabetes and other diseases characterized by defective oxidation and increased carbon dioxide of the blood, phosphorus poisoning, severe anemias, pneumonia.

The Red Corpuscles.—Variation in Number.—We have already laid stress upon the fact that moderate increase or decrease in the number of erythrocytes per cubic millimeter gives us no sure information unless at the same time we determine the total volume of blood; such change may be brought about by concentration or dilution of the blood plasma as well as by actual increase or decrease in the number of circulating corpuscles. There may be an apparent great increase in the red cells in cholera asiatica, due to draining away of the fluid from the blood, or, on the other hand, an actual **polycythemia.** A great increase in the number of red corpuscles is seen in those living at high levels, and this without recognizable diminution in the total volume of the blood. What is the cause has not surely been determined. Even in a balloon ascent to an altitude of several thousand feet an increase from the normal 5,000,000 to 8,500,000 has been recorded. A similar increase has been recognized in animals made to breathe carbon monoxide. This suggests that the change is adaptive, due to increased demand for oxygen, and that it is brought about by an increased outpouring of erythrocytes from the bone marrow.

A pathological polycythemia has been recorded by several observers, unconnected with change in altitude, blood counts affording from 8,000,000 to 14,000,000 corpuscles. There is often an associated enlargement of the spleen, and a dusky or cyanotic appearance of the skin, with, at post mortem, presence of abundant red marrow. The cause of the condition is practically unknown. Death often occurs within a few weeks of recognition of the state, although a few cases of return to normal have been noted.

Variations in Size.—Where there is disturbance in the production of red corpuscles, as in secondary and pernicious anemias, certain corpuscles may attain large size (**megalocytes**), with a diameter of from 16 to 20μ in place of the normal 7 to 8.5μ. In the same conditions we may also encounter cells that are abnormally small (**microcytes**), along with corpuscles exhibiting great variation in shape (**poikilocytes**, from ποικίλος, various).

Variations in Structure and Staining Reactions.—A study of the red marrow shows that the red corpuscles originate from nucleated cells —erythroblasts—by a process of gradual shrinkage of the nucleus, with discharge of nucleoli or nucleolar matter into the cytoplasm, which at first scattered in masses, gradually diffuses evenly through the whole cytoplasm. In disease we may encounter various modifications of the corpuscles which represent stages in their development and indicate, therefore, an increased activity of the marrow, with premature discharge of the corpuscles. We thus, at times, encounter nucleated red corpuscles in the form of **megaloblasts**, large cells with large pale nuclei (the earliest stage), **normoblasts**, which are hemoglobin-containing cells of normal size, but nucleated, and other cells exhibiting **polychromatophilia**, certain corpuscles taking on a more basic, purplish stain. By Romanowsky's stain or modifications of the same this is characteristic of immature erythrocytes. The "stippling" of the red corpuscles, seen in some cases of lead poisoning, may also indicate an incomplete conversion of discharged nucleolar matter into hemoglobin, and may also be evidence of immaturity. As regards irregular staining, it must be noted that this may also be met with in cases of recognizable degeneration of the corpuscles (*e. g.*, in early thrombi).

Other clear evidences of disintegration of the corpuscle are seen in the conditions of **plasmorrhexis** and **plasmoschisis**. The former is the development of crenations at the periphery, with progressive liberation of peripheral globules of varying size. The latter is the rapid breaking up of the whole body of the corpuscle into small globules from which the hemoglobin has been discharged, so that as they separate they are scarce distinguishable from blood platelets.

Variations in Hemoglobin Content.—There may be great variation in the color index of the blood, *i. e.*, the ratio of the hemoglobin per corpuscle. The color index may be calculated as follows: Multiply the first two figures of the red count by two for the hemoglobin figure: thus, 5,000,000 corpuscles normally give 100 per cent. hemoglobin, and 1,000,000 corpuscles 20 per cent. hemoglobin. The color index is the value of the fraction whose numerator is the actual hemoglobin figure and whose denominator is the figure that one might expect from the corpuscular count. If the count be 3,500,000 and hemoglobin 60 per cent., the color index will be $\frac{60}{70}$ or 0.8; if the count be 2,000,000 and hemoglobin 55 per cent., the color index will be $\frac{55}{40}$ or 1.4. The color index is, for example, found increased in pernicious anemia, reduced in chlorosis. There may be both a reduction in the hemoglobin produced, as in the

latter case—a defective conversion of the nuclear matter of the erythroblast into hemoglobin, and, on the other hand, a diffusion of the hemoglobin out of the corpuscle or **hemolysis.** We possess numerous agencies which can bring about hemolysis both within the vessels and in the test-tube: cold (as in paroxysmal hemoglobinuria), heat (as in burns), the sera and tissue extracts of animals of other species, and sometimes of those of the same species, experimentally produced hemolytic sera (p. 161), certain bacterial toxins (which possibly explain the anemia of many infectious diseases), notably those of streptococcus, B. coli, pyococcus aureus, pneumococcus; vegetable products, such as ricin and amanita (mushroom) poison. In addition many chemical agents bring about this diffusion of hemoglobin and "laking" of the blood, notably pyrogallic acid, glycerine, potassium chlorate, and toluylene-diamin. And by employment of one or other of these agents we can materially reduce the number of circulating erythrocytes. The red corpuscle, that is, when it has lost its hemoglobin, has no power to reproduce it, and so is rendered largely useless. Its stroma is removed by the agency of the spleen. Thus, by inoculating rabbits with repeated non-lethal doses of B. coli (Charlton), or by similar doses of ricin (Bunting), the number of erythrocytes becomes reduced to 1,000,000 or less per c.mm., and conditions (including poikilocytosis) closely simulating pernicious anema are produced.

Secondary Anemias.—When we can determine what appears to be an adequate cause for the reduction in the total number of corpuscles, we speak of a secondary anemia. This may be **acute,** as after profound loss of blood, potassium chlorate poisoning, and severe infections, or **chronic,** as after recurrent small hemorrhages, in splenic anemia, cancer, and exhausting diseases, lead poisoning, intestinal parasites, etc. The longer continued the destruction or loss of red corpuscles, the greater the strain upon the marrow and blood-forming organs, with the result that nucleated and other premature and imperfectly formed erythrocytes are apt to appear in the circulating blood until finally, as in those afflicted with the fish tapeworm (Dibothriocephalus latus), or in some cases of cancer, the blood picture is indistinguishable from that of pernicious anemia.

Pernicious (or Addisonian) Anemia.—This affords a very characteristic picture. The victim has a peculiar lemon yellow color, is apt to be flabbily fat, exhibits progressive muscular weakness, with weak heart action, achlorhydria, (absence of free acid in the gastric juice), and other digestive disturbances, diarrhœa, etc. There may be one or two remissions, but with very rare exceptions the course is fatal within less than two years. The blood condition is striking: marked reduction in the number of erythrocytes, it may be, down to 500,000 per c.mm.: presence of poikilocytosis, with macrocytes, microcytes, and nucleated red corpuscles. The color index is increased.

At autopsy the most marked features are the bright yellow color of the body fat, the small amount and thin, watery character of the

blood, the pallor and bloodlessness of all organs; œdema of tissues and fluid in the serous cavities: the fatty degeneration of the heart muscle; the presence of increased iron in the liver demonstrated by Quincke's (Prussian blue) or Perl's (sulphide of iron) test, and evidences of hyperplasia of the red marrow of the bones. Sometimes there is an accompanying atrophic gastritis, and evidence of interference with the sensory tracts in the lower part of the cord.

These various conditions suggest the continued action of a hemolytic toxin of gastro-intestinal origin, leading to excessive destruction of the red corpuscles, increase in hepatic iron, and increased but imperfect compensatory production of corpuscles. The increase in hepatic iron, for example, is a result of hemoglobin disintegration; the pigmentation of the fat, a result of modification of the hemoglobin liberated in the circulating blood. Whether the fatty degeneration of the heart muscles is of toxic origin or due to deficient oxidation is uncertain.

The cause of the hemolysis is still undetermined; there may be more than one. From the frequent association of **pyorrhœa alveolaris**, a low form of suppuration involving the sockets of the teeth, Hunter inclines to the view that a secondary chronic streptococcic gastritis is the essential cause; one of us (Adami) has suggested that we deal with a subinfection by means of hemolytic intestinal bacteria of the colon group; Herter would implicate the excessive proliferation of the B. Welchii in the lower intestine. Based upon the close resemblance between the clinical picture and post mortem appearances in man and those of surra and dourine in the horse, the latest hypothesis is that we deal with a condition of trypanosomiasis. The riddle has still to be solved.

Aplastic Anemia.—Rarely there is encountered an extreme anemia accompanied not by hyperplasia, but by an hypoplasia of the bone marrow and hemopoietic centres. There is great reduction in the number of red corpuscles, absence of normoblasts and megaloblasts (immature erythrocytes), low color index. Poikilocytosis is not marked, lymphocytes are in good number, but leukocytes (polynuclears and eosinophiles) fewer than normal. Instead of increase in red marrow there is reduction, its place being taken by fat cells.

Chlorosis.—Chlorosis is an anemia of a different order affecting young adult females; its presence in young males is so rare that many deny its existence. There is a characteristic pallor, the "green sickness" of Elizabethan writers, lassitude with weakness following upon slight exertion, dyspepsia and capricious appetite, gastric acidity, constipation and attacks of palpitation.

The blood exhibits definite hydremia with corresponding reduction in the number of erythrocytes per c.mm. What is most marked is the reduction in the hemoglobin, so that the color index averages 0.5, and may be as low as 0.1. The good effects that follow the proper exhibition of iron suggest that imperfect production of hemoglobin is the essential feature. What leads to this we do not know, although several clinicians

have laid stress upon constipation and the good effects that follow a course of laxatives, suggesting intestinal intoxication as the underlying cause. Others see a relationship between the sex of those affected and between aberration of the menstrual function and these blood disturbances.

The Leukocytes.—Before proceeding to describe the changes that occur in the leukocytes it is necessary to classify these and to have some idea as to the relationship of the different forms. Now this is not an easy matter, and that because, despite abundant research, there is still active controversy regarding many points, and to discuss the *pros* and *cons* would occupy many pages. We can, therefore, but give dogmatically our own opinions regarding these matters, stating frankly that these represent one view, and that they are liable to revision.[1]

Briefly, we have to distinguish between the circulating white corpuscles and those found outside the vessels and in the tissues, certain wandering cells being found in the one region and not in the other. We can further distinguish between those white corpuscles, or wandering cells which originate from myeloblasts, those that originate from lymphoblasts and lymphoid tissue, and those originating from endothelial and other connective-tissue elements. The trend of recent observations is to approximate more and more the last two groups. The difficulties in making a classification depend essentially upon this, that the earliest and simplest stages of developing cells show practically no differentiation, and thus it becomes a matter of extraordinary difficulty to trace back the different forms of cells to their origins, particularly when in the hemopoietic system the different orders of cells are apt to originate side by side and not from different isolated centres.

Forms of Leukocytes.—We may, however, distinguish the following main forms:

Of myeloblastic origin (granular leukocytes): (1) **the polymorphonuclear, polynuclear,** or **neutrophile** cell. This is the commonest white corpuscle of the circulating blood, constituting in general more than 65 per cent. of the white corpuscles present in normal blood. In its cytoplasm are fine granules which stain with neutral or more accurately weakly acid dyes. It is the form in greatest abundance in acute inflammation, and is thus the typical *pus cell*. The nucleus is characteristically lobate, so that under low power the cell appears to be multinucleate. It is actively phagocytic, particularly for bacteria. It rarely shows evidence of mitosis in the blood stream, or again in the tissues at the site of inflammation. It has nothing to do with tissue formation.

The Eosinophile.—This is of the same size as the former, most often its nucleus is coarsely lobate or horseshoe-shaped. In the cytoplasm are granules much coarser than those of the former, and these take an intense stain with eosin and other acid aniline dyes. It also migrates

[1] A fuller discussion of the subject will be found in the small work on "*Inflammation*," published by one of us (Adami). (Macmillan: London and New York, fourth edition.)

out of the vessels in the early stage of acute inflammation, but is soon overpassed in number by the polynuclears, while again it is found in the tissues in fair numbers in certain forms of subacute inflammation. In normal blood this form is present in but small numbers (about 3 per cent.). It is abundant (10 to 50 per cent.) in many forms of helminthiasis (parasitic worms), in certain cases of chronic skin disease, etc. Only rarely is it observed to act as a phagocyte. Studies made on the frog and other animals show that these cells can discharge their granules, which are of nucleoproteid nature. The cells seem thus to have certain excretory functions. Opie has noted that during the course of certain acute peritoneal infections the eosinophile disappears largely from the peripheral circulation, but may be found accumulating in the mesenteric and other vessels, and there undergoing migration.

The Lymphocytes.—The typical lymphocyte is distinctly smaller than the preceding form, possessing a relatively large, spherical, deeply staining nucleus, with a relatively inconsiderable surrounding layer of cytoplasm. This form of cell is but slightly amœboid. It is not observed to be phagocytic. In inflammatory conditions it is found more particularly accumulated around the vessels. There is still doubt as to whether these accumulations are the result, in the main, of migration, or are due to proliferation of preëxisting lymphocytes of the region (Marchand). In subacute and chronic inflammation (*e. g.,* tuberculosis) this is the preponderating type of cell present. In the blood stream in pathological conditions, what are known as large lymphocytes, one form of "large mononuclear," may be encountered; these represent immature lymphocytes. In the tissues in cases of subacute inflammation the small lymphocytes give origin to cells of larger size, with excentric nucleus and a somewhat polygonal cell body of fair size, the *plasma cell* (p. 130).

Mast Cells.—These cells, rare in the normal blood, may be occasionally encountered in pathological states, such as leukemia. They are of fair size and possess abundant granules which take a basic stain and are so large that they may be taken for clusters of micrococci. The nucleus is generally degenerated. Whether the mast cells in the tissues are of the same origin as those in the blood has not been absolutely determined, but there they may take on motility, and their path may be traced occasionally by the granules which they have shed. In any position they are comparatively rare.

Hyaline Cells.—Cells having a large body and an oval, pale staining nucleus, constituting "large mononuclears," are encountered in the blood in small numbers, and there are difficult to distinguish from the large lymphocytes already described. Their cytoplasm is free from granules. A similar type of cell is seen in conditions of inflammation of the peritoneal cavity, and here clearly some at least of these cells are of endothelial origin, derived from the lining endothelium of the serous surfaces. It is possible that the intravascular form originates from the vascular endothelium (Fig. 27). The **macrophages** of the sinuses of in-

flamed lymph nodes are of this order. This type of cell is phagocytic, not for the bacteria of acute disease, but for other cells and their debris, and it is generally held that it is capable of becoming fibroblastic and so of leading to the formation of connective tissue.

Leukocytosis. — The presence of an excessive number of any one or more of the above forms in the blood constitutes a condition of leukocytosis. We distinguish thus: (*a*) polynuclear leukocytosis or a neutrophilia, (*b*) eosinophilia, (*c*) lymphocytosis, and (*d*) myelocytosis, or the presence of aberrant or immature forms. **Leukemia** is a condition of excessive leukocytosis where the number of leukocytes usually exceeds (say) 50,000 per cubic millimeter. The number of leukocytes of various orders present in normal blood is in the neighborhood of 5000 per c.mm., but there may be a considerable physiological variation. Thus young individuals exhibit a well-marked relative leukocytosis of 12,000 to 15,000 during the first week of life, of 10,000 to 12,000 during the first ten years. Toward the time of parturition in the female the number is apt to reach 15,000 to 20,000. After a rich protein meal there occurs a moderate *alimentary* leukocytosis. During the last hours of life a *terminal* leukocytosis is generally to be recognized.

Polynuclear Leukocytosis is met with in inflammatory and many infectious conditions; not, however, in all, for it is absent in typhoid, malaria, and the more ordinary type of chronic tuberculosis and leprosy, save where there is secondary infection. So, also, it is wanting in measles, mumps, and in most cases of influenza. It is very pronounced in pneumonia, where there may be a leukocytosis of even 100,000, with 95 per cent. of polynuclears. Suppurative disease and local and generalized disturbances due to pyogenic organisms exhibit this type of leukocytosis. It is of note also that in states characterized by grave disturbance of the liver, and where there is a breaking down of tissues, as in the later stages of carcinoma, this form shows itself. Antipyretics and salicylates induce a moderate grade.

Eosinophilia is seen in many different forms of helminthiasis (p. 92), in many irritative skin diseases, accompanying myelogenic leukemia, in bronchial asthma, hay fever, and allied conditions of so-called idiosyncrasy, in some post-febrile states, and in a variety of conditions it is difficult to correlate.

Lymphocytosis is frequent in young children, particularly where there are gastro-intestinal disorders; it may be noted that in the young there is a relatively great development of the lymphoid tissue of the body, and especially of the intestinal area, and irritation of the lymph nodes is accompanied by a greater discharge of lymphocytes into the blood. A similar lymphocytosis is found in adults, where there are enlarged lymph nodes. With whooping-cough, lymphocytosis is so marked as to be pathognomonic. In scurvy, rickets, sclerosis, and debilitating disease a lymphocytosis of moderate grade is frequently noticeable.

Leukemia. — Leukemia is a disease characterized by the *continued* presence of an excess of circulating leukocytes; there may be no more than

15,000 per cubic millimeter, although generally there are hundreds of thousands. The state is characterized by progressive weakness and associated anemia proper, usually with a greatly enlarged spleen. There are, however, two types—the myelogenous or myeloblastic and the lymphatic.

Myelogenous Leukemia.—This form is seen most often in early adult life, and more often in the male. The underlying feature is an aberrant hyperplasia of the blood-forming tissues. The bone marrow is always affected, showing an excess of gray marrow, in which abundant cells can be found exhibiting transitional stages, from myeloblast to myelocyte, to the neutrophile leukocyte. There is an associated increased development of eosinophiles, evidence of increased activity also in the production of red corpuscles, with increase in the number of megacaryocytes.

The spleen also reverts to the condition seen before birth, and presents indications of active formation of myelocytes. The organ may attain an enormous size. There may be similar indications of myelocyte formation in the liver. In all these areas there is but slight indication of an increased activity of the lymphoid tissue proper. The most striking change is seen in the blood, where there may be an extraordinary increase in the number of white corpuscles, varying from 60,000 to as many as 1,500,000. The greatest increase is in the immature granule cells or myelocytes, which may compose half of the total, the neutrophiles or polynuclears constituting almost the other half. There is generally a pronounced eosinophilia, some increase in the number of mast cells, and the lymphocytes, although relatively in small numbers, are present in greater numbers than in health. With this there is a distinct, though not an extreme increase in the number of red corpuscles. These large and abundant leukocytes tend to clog the capillaries of organs, and this, with the reduction in the number of red corpuscles, may explain the dyspnœa, general bodily weakness, and wasting, which are features of the disease, as again the epistaxis, retinal, and other hemorrhages. Associated with the increased production there are evidences of increased destruction of the leukocytes, notably an excessive discharge of uric acid, which we assume to be due to the disintegration of the nuclei of these cells. The disease is chronic, lasting from a few months to several years after its first recognition.

Lymphatic Leukemia.—This also occurs in young adult life and mainly in the male, although found at all ages. In young people the disease tends to have an acute onset and course. Here not the spleen but the lymph nodes are most involved. The symptoms and physical signs are otherwise much the same as in the other form, and blood films show a great excess of lymphocytes (see plate) of typical shape, with large deep-staining nucleus and small rim of cytoplasm. In the acute form they are of more atypical and embryonic type, resembling thus the lymphoblasts, and showing a less deeply staining nucleus of irregular shape, with relatively abundant cytoplasm.

PLATE XI

Myelogenous Leukaemia. Blood from an acute case.
(Cabot.)

Whether all these cells are lymphoblastic is a matter of present debate. It has recently been shown that the presence of **Altmann's granules** in cells of this order is not, as Schridde held, a positive indication of lymphoblastic origin, for such granules may also be detected in myeloblasts. Thus it is quite possible that there exists an acute leukemia, due to excessive atypical development of the myelocytic elements, indistinguishable by present methods of research from the acute lymphatic form. Or, expressed otherwise, there may be an acute leukemia characterized by the overgrowth and discharge into the blood of cells representing the common primary stage of both lymphocytes and granular leukocytes.

Unlike the myelogenous type, in the lymphatic there is a liability to the appearance of multiple, minute, subcutaneous lymphoid nodules. Unlike the other form there is here characteristically an accompanying febrile state (102° to 104° F.), with severe sweats, and development of a "typhoid state." The condition is fatal, and of shorter course than the other form; and this, although the blood picture does not exhibit such extreme changes, the number of contained white cells averaging 200,000; eosinophiles and mast cells are wanting, nor is there any marked increase in the neutrophiles.

Blood Platelets.—To the other constituents of the blood brief reference may be made. We have already referred to the importance of the blood platelets in the development of thrombi. These are small bodies, oval or pear-shaped, averaging 2μ; in blood smears they tend to be present in small groups. Even in normal blood they show considerable variation in their number, from 200,000 to 700,000 per cubic millimeter. As to their origin there has been much debate, but since J. H. Wright's studies there can be no doubt that some at least are derived from the giant cells (megacaryocytes) of the bone marrow. We ourselves still hold to the belief that in certain forms of thrombosis a condition of plasmoschisis results in the breaking up of the red corpuscle into oval bodies which are indistinguishable from the platelets of normal blood. It is deserving of note that in certain conditions, *e. g.*, pernicious anemia, there is commonly a marked diminution in the platelets. In some cases of purpura also they have been found wholly absent. In pneumonia and in myelogenous leukemia they are increased in number.

Still smaller elements, the **dust bodies** or **hemoconia**, are to be recognized in the blood. Nicholls and others regard these as products of disintegration, more particularly of the erythrocytes.

The Lymphatic System: Œdema.—The accumulation of serous fluid transuded from the vessels in the tissue spaces and cavities of the body constitutes the condition of œdema. Distinct names are given to such accumulation of fluid in particular areas; thus **anasarca** or interstitial œdema is the accumulation in the tissue spaces of the limbs and body wall. **Chemosis** is the serous infiltration of the subconjunctival tissue. **Ascites** is the accumulation of serous fluid in the peritoneal cavity;

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hydrothorax, in the pleural cavity; **hydropericardium**, in the pericardial; **hydrocele**, in the tunica vaginalis testis; **internal hydrocephalus**, in the ventricles of the brain; **external hydrocephalus**, distending the spaces of the pia arachnoid. We would lay down that accumulations of serous fluid in communication with the exterior, and thus outside the body, are not strictly œdema; **pulmonary œdema**, therefore, the accumulation of fluid in the air sacs of the lung is, strictly speaking, not a member of this class.

· Our classification of these various conditions has so far been faulty. Recent studies show that the lymphatic channels originate from the venous system and form a closed, freely branching series of ducts separated by an endothelial lining from the tissue spaces. As to the relationships of the great serous cavities of the body with this system there is still debate, some holding (from the ease and rapidity with which milk globules, red corpuscles, etc., pass from the peritoneal cavity into the lymphatic vessels of the diaphragm) that there is a direct communication; others, from histological considerations, deny the existence of any such free communication. For convenience, therefore, we may regard the three areas as distinct, and lay down that serous fluid may become accumulated (1) in the lymphatic channels proper, (2) in the serous cavities of the body, and (3) in the tissue spaces. Nay, more, we can go farther and recognize (4) that fluid may accumulate abnormally in the individual cells. (See Serous Atrophy and Hydropic Degeneration, pp. 264 and 272.)

1. **Lymphangiectasis.**—Little need be said regarding the first of these conditions. We recognize that, in consequence of obstruction, whether congenital or as the result of disease affecting the efferent lymphatic channels of certain organs or areas, there may result a huge distension of the lymph channels behind the point of obstruction, a distension so great that at times they take on a cystic appearance, forming lymph cysts. Such distension is seen in congenital conditions, such as **macroglossia** and **macrocheilia** (p. 398). **Hygroma** of the neck may be regarded as of similar nature (p. 398). As an acquired condition, lymphangiectasis is encountered in one group of cases of elephantiasis.

2. **Accumulation in the Serous Cavities, etc.**—Serous cavities are lined throughout by an endothelium. There is thus normally no direct communication between them and the tissue spaces of the organs contained in those cavities. Thus, an œdematous condition of the intestinal walls, for example, is not necessarily followed by ascites, and *vice versa*. But while this is the case, we must recognize that there is a constant circulation of fluid through these cavities, passing into them through the endothelial lining and passing out through stomata or areas of thinning in particular areas. Thus pigmented matter or bacteria introduced into the peritoneal cavity finds a way within a few minutes into the substernal and other lymph nodes.

In cases of inflammation there may be rapid and abundant accumu-

PLATE XII

FIG. 1
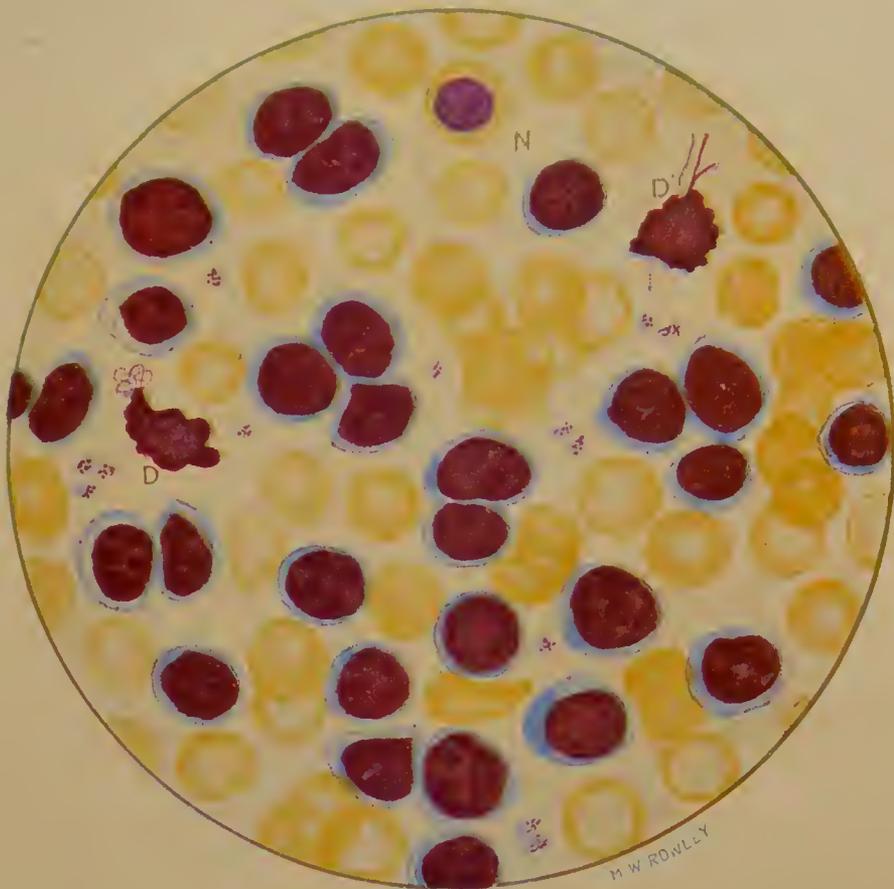
Chronic Lymphatic Leukemia (Actual Field). (Cabot.)

small lymphocytes. D, D, regenerating lymphocytes. N, normoblast.

Acute Myelogenous Leukemia (Actual Field). (Cabot.)

M, neutrophil. L, lymphocyte. A, P, N.

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lation of fluid in these cavities. This inflammatory exudate is more than a simple serous effusion; whereas its salts approximate in concentration to those of the blood serum, the inflammatory exudate is much richer in proteins than is non-inflammatory ascitic fluid. Very extensive accumulations of fluid occur in the various serous cavities as a result, either of obstruction to the onward flow of blood, as in heart disease and conditions of portal obstruction, or, again, as a result of an impoverished condition of the blood without actual obstruction to onflow, but with enfeebled circulation and depressed nutrition.

3. **Anasarca.**—Remembering what has been said regarding the want of relationship between the tissue spaces and the lymph channels it will be seen that two main factors determine the accumulation of fluid in the tissue spaces: (1) the rate of escape of fluid out of the blood vessels into the tissue spaces; (2) the rate of escape of fluid from the tissue spaces into the lymphatic channels. If fluid can be carried off by the lymphatics as rapidly as it passes out from the blood, no accumulation can occur. In other words, an œdematous state may be brought about by an excessive discharge from the blood, or, on the contrary, by defective drainage away through the lymphatic channels.

There has been controversy extending over long years as to the relative importance of the different factors found associated with the production of the œdematous state. On the one hand, there are those who would reduce the problem to its very simplest physical factors, who regard the lining wall of the vessels as nothing more than a filtration membrane, who thus ascribe œdema in the main to pressure differences, to increased discharge from thinned and dilated capillary and other vessels. On the other hand, an important body of investigators holds that the endothelial cells lining the blood vessels are not merely membranes, but possess a selective capacity, and thus regard the œdema fluid, not as a filtrate, but as determined by the state of nutrition of the vessel wall. Neither of these schools seems to have paid sufficient attention to the problem of how, once in the tissue spaces, the fluid gets into the lymphatic channels. A compromise may be reached. We must admit that when the smaller vessels become dilated their walls become thinned and the intercellular spaces of their endothelium become enlarged, so that if there be any increased pressure all conditions favor an increased transfusion of fluid between the cells; but we must admit also that the endothelium lining the vessels is by no means an inert cell layer. Thus the dilatation of vessels is not by any means necessarily a purely mechanical matter; we must admit that malnutrition of the capillary endothelium and lowered vitality of the same is a factor favoring œdema.

We may possibly go farther than this. Studies upon the mammary gland in its stage of activity indicate that through the capillary endothelium there is a selective removal of fatty matters from the blood for the use of the mammary gland cells, and the reason for the difference between a serous and inflammatory exudate, as again between

the composition of cerebrospinal fluid, aqueous humor and ascitic fluid, must largely be this difference in the selective activities of the vascular endothelium in these different regions.

The last few years have seen another principle invoked to explain œdema. It is well known that the rate and the direction of osmosis depends upon the relative concentration of salts on either side of the osmotic membrane, and the ascites and the anasarca encountered in cases of nephritis have been ascribed to heaping up of sodium chloride within the tissues and tissue spaces. Some physicians have found marked reduction in anasarcous states following the reduction in the amount of chlorides given as food. Lately, Prof. Fischer has propounded yet another theory to explain this accumulation of fluid in the tissues, a theory based upon the properties of colloidal bodies like gelatin and presumably other proteins. If, for example, dried gelatin be placed in plain water, it will absorb a definite quantity of that water and swell up to a certain point. If, however, the water be weakly acidified the amount absorbed becomes very much greater. If a freshly removed sheep's or ox's eye be placed in ordinary water, nothing very much happens; if it be placed in weakly acidulated water the amount of fluid taken up, apparently by the vitreous, is so great that the eyeball is liable to undergo rupture. If, again, a frog's limb be ligatured or cut off and now be placed in the water in which previously the frog had been swimming, there occurs an intense imbibition of fluid, with development of post mortem anasarca. As we know, when muscle and other tissues die they become increasingly acid. It is to this acidity that Prof. Fischer ascribes the imbibition in this last case, and he is inclined therefore to ascribe many cases of œdema and anasarca not to mechanical changes in the blood pressure or, again, to changes in the blood itself, but to alterations in the colloidal tissue elements, whereby these need and attract to themselves increasing fluid. The idea is suggestive; we cannot, however, see that it covers the whole ground; rather we would say that we continue to recognize the following types:

Types of Œdema.—1. **Congestive Œdema.**—This is the commonest form and is met with in cases of obstruction to the venous outflow. Here, undoubtedly, there is (*a*) increased capillary pressure, (*b*) dilatation of the capillaries, with thinning of the walls, (*c*) slowing of the blood stream and increased venosity of the blood, (*d*) lowered nutrition and vitality of the capillary wall. Possibly here, secondarily, the nutrition of the tissues and the changes occurring in those tissues form a factor. Thus ligature of the main vein of a limb in a healthy animal is not followed by œdema, though such œdema will occur if the animal be in an impoverished state of health.

2. **Œdema from Lymphatic Obstruction.**—It has already been noted that lymphatic obstruction, while leading to dilatation of the lymphatic vessels, does not necessarily cause œdema, in fact experimentally the main lymphatics of a part may be ligatured and yet no œdema may occur. The blood capillaries are capable of taking up fluid from the

tissues just as they permit fluid to pass into them. But sometimes œdema results, and here again the condition of the tissues appears to be a factor. We may find, for example, œdema of the arm occurring in the later stages of cancer of the breast, when all the axillary lymphatics have become involved; but in the earlier stage all those lymphatics may be excised, in order to arrest the extension of the disease, and no œdema shows itself.

In this connection we may note three varieties of ascites, viz., **chylous, chyliform,** and **pseudochylous** ascites. The first of these is due to rupture of the abdominal lymphatics, or of the receptaculum chyli, whereby the milky chyle escapes into the peritoneal cavity. Of similar origin is **chylous hydrothorax** from rupture of the thoracic duct, and **chyluria,** from rupture of the lymphatics of the pelvis of the kidney or of the bladder. **Chyliform ascites** is found in cases of abdominal carcinoma or tuberculosis, the emulsion of fat giving the milky appearance, and is due to breaking down of leukocytes and other cells that have undergone fatty degeneration. The percentage of fat in these cases may be much higher than in the former. In **pseudochylous ascites** the milky appearance is associated with absence of fat, and is brought about either by mucoid substances or suspended proteins.

3. **Inflammatory Œdema.**—All acute inflammation is accompanied by a local increased passage of fluid out of the vessels. The fluid in these cases approaches more nearly in its composition to the blood plasma than does that of congestive œdema. As will be remembered, the capillary endothelium shows a striking series of changes in acute inflammation, and to this changed condition we must largely ascribe the increased exudate, although here also we must recognize that the tissue cells in the involved area exhibit marked disintegrative changes which may undoubtedly attract more fluid.

4. **Toxic Œdema.**—We know, experimentally, that there are substances which act as lymphagogues, inducing increased lymph formation. In the case of some of these no noticeable change is exerted on the circulation. The difference in the distribution of the anasarca in heart and kidney disease, respectively, would suggest that the toxic substances circulating in the blood have possibly a different effect on the capillary wall in the diverse conditions.

5. **Neuropathic Œdema.**—We have already emphasized on more than one occasion, that the central nervous system of itself can set up disturbances of the same character as those due to the action of local *noxæ.* The same is true in connection with this matter of œdema. This is well seen in **herpes zoster,** where irritation of one posterior spinal ganglion is followed by œdema accurately mapping out the superficial area supplied by that particular spinal nerve. There also occur certain remarkable **angioneurotic œdemas,** characterized by the sudden pouring out of fluid into particular areas of the internal organs or skin, without any recognizable cause. It is true that these resemble much the urticaria and localized œdema seen in cases of idiosyncrasy and food-

poisoning, conditions which we have noted (p. 113) are in turn allied to anaphylactic phenomena. It may eventually be determined that in these we deal with something more than simple uncomplicated vasomotor disturbances.

6. **Hydrops ex Vacuo.**—Finally, accompanying the atrophy of tissues enclosed within spaces having relatively resistant walls, there may be a "**replacement dropsy.**" The most familiar example of this is noted in senile and other atrophies of the brain where there may be marked accumulation of fluid, either externally in the pia arachnoid spaces, or internally in the ventricles, or both. Hemorrhagic and necrotic cysts (p. 413) belong to the same category.

THE HEART, BLOODVESSELS, AND LYMPHATIC VESSELS

THE HEART: GENERAL CONSIDERATIONS

The striking progress made during the last few years in the comprehension and treatment of heart disease have been preëminently advanced by the study of normal and perverted function. For such a study, it is true, a knowledge of the anatomy and histology, and, indeed, of the embryology of the organ has been a prerequisite, but undoubtedly at the present time a knowledge of the pathological physiology of the heart is of profound importance to the medical man. Thus of necessity a chapter must be devoted to cardiac function and its disturbances.

Functionally the heart is nothing more nor less than a pump—a double pump and double-actioned—the indications being that the filling of the ventricles is not a passive process, but in part at least active, due to suction exerted by the expanding ventricles; it is a suction pump, even if, to a greater extent, it is a propulsive organ. With this it is extraordinarily responsive to variations in the work it is called upon to accomplish, altering its rate or rhythm and the force of individual beats according to the amount of blood supplied, the resistance against which the blood is propelled, and the stimuli received from the nervous centres. We must, even if rapidly, mention in order the varying factors which modify its activity, taking for granted a knowledge of the main outlines of its anatomy and embryogeny.

It is a matter of difficulty to determine the order in which to treat the various sections of our subject, and this because there is such an intimate interaction between the work and the disturbances of the different portions of the heart, that it is impossible to discuss one phase of heart action without referring to the other. The following, however, may be found helpful:

1. **The Auricles.**—We must regard the auricles as distensible pouches with relatively weak muscular walls. Their very structure indicates that they act as reservoirs to accumulate blood during ventricular systole

and deliver it freely into the ventricles during their diastole. It is true that these walls are muscular, true further, as has been abundantly demonstrated during the last few years, that the heart beat commences at the sino-auricular ring, where the venæ cavæ open into the auricle, and from there the contraction spreads through the auricle, and so later to the ventricles; but in the auricles the contraction is relatively feeble. Under normal conditions there is indeed very little need for vigorous contraction. The very size of the auriculoventricular orifice, as we shall point out, and the active dilatation of the ventricles together afford an easy flow of blood into the ventricular chambers—a flow so easy that no proper valves are present at the orifices of the venæ cavæ and the pulmonary veins respectively. At most, with the contraction of the circular musculature around each orifice, there is a diminution in their lumen. It thus becomes a matter still under debate as to whether with each auricular systole some small amount of blood is not driven backward into the veins. As already noted, the flow forward into the ventricles is so easy that if normally such regurgitation is present, it is not propagated, and does not, for example, show itself in the neck veins.

2. **Venous Pulse.**—If, however, there be obstruction to the onflow of blood and dilatation of the auricle, such regurgitation easily manifests itself. There have been numerous conflicting studies upon this matter during the last century. We owe, more especially, to Dr. James Mackenzie and his employment of the polygraph (*i. e.*, of an instrument permitting simultaneous records of venous pulse, apex beat, arterial pulse, etc.) that today we recognize the different forms of venous pulse and are able to translate the significance of the same. Mackenzie has shown very clearly that according to their position relative to the phases of the carotid pulse, we may recognize three separate waves in the venous pulse (*e. g.*, in that seen in the jugular vein).

I. If the auricle be distended and its contraction be powerful, there may be propagated along the vein a wave corresponding with the auricular systole.

II. If the auriculoventricular valve be incompetent there may be propagated backward a regurgitant wave corresponding in time with the ventricular systole, and

III. Owing to the close proximity of the carotid and jugular within the same sheath, an active impulse propagated along the carotid artery may be transmitted to the column of blood in the vein showing itself a little later than the regurgitant ventricular wave.

Sometimes all three of these waves are present together. Where there is little or no regurgitation through the tricuspid, the auricular systolic wave alone may be present, as in the rare condition of tricuspid stenosis. Where the tricuspid is markedly incompetent, and through regurgitation the right auricle is overdistended and enfeebled so that its systole is much weakened, then the ventricular systolic wave may be of great size, the other two scarce recognizable.

In other words, a careful study of the venous pulse is affording us valuable evidence regarding the state of the right heart, as compared with that of the left. The indications are that regurgitation of blood into the veins is relatively common, that, as King showed long ago, it acts as a factor of safety, preventing excessive strain upon the delicate auricles, as again upon the weak right ventricle. We shall have more to say regarding regurgitation and auricular function in connection with our next section.

3. **The Auriculoventricular Valves.** As already noted, the most striking feature of these valves is their relatively large size, so that their orifices permit an easy filling of the ventricles in diastole, and this without resistance. The very size of the orifices demands a special mechanism, so that during systole the pressure on the under surfaces of the large valve flaps does not make them give way and allow escape into the auricular chamber. This mechanism is afforded by the papillary muscles and the chordæ tendineæ. The chordæ are attached in rows to the under aspect of each valve, and originate from the papillary muscles in such a way that each muscle gives origin to chords passing to each valve flap. They are further so attached, some to the very edge of the valve, others to the under surface, that when the valve flaps are ballooned up by the pressure of blood in the ventricle, the flaps are not absolutely flat, but have a marked convexity upward in such a way that the distal or terminal border of the main flaps does not meet the edge of its fellow, but there is apposition of the auricular aspects of the terminal portions of these valves, and in this way the greater the pressure within the ventricle the more firm is the closure of the valve.

As to the action of the papillary muscles, there is this to be noted, that in systole it is the breadth and not the length of the ventricles that undergoes serious alteration. Were the papillary muscles to contract simultaneously with the ventricular wall while the ventricle is still distended, the tendency would be to keep the valve open and favor regurgitation. Roy and Adami have shown that the papillary muscles are the last portion of the ventricular wall to undergo contraction. It would thus seem that these muscles come into action after the increasing pressure within the ventricle in systole has led already to the apposition of the flaps, and that by their contraction they prevent excessive ballooning of the valve into the auricular chamber. They and other observers have shown that the papillary contraction may be irregular or may be wanting, and have associated these irregularities with other disturbance in the heart action. The main cause, however, of regurgitation, is distension from an overfilling of the ventricle. This we shall discuss in our next section.

The Ventricles.—These are essentially the pumping apparatus of the heart, and their structure in this relationship shows certain interesting features. Each ventricle does not contract as a sphere and thus become narrowed in every direction. The layers of muscle are so arranged that with contraction the length is practically unaltered,

so that in systole relatively little internal pressure is exerted upon the apex, which, indeed, is singularly thin. The arrangement of the fibres and their mode of contraction are such that the walls of the apical portion of either ventricle, and particularly of the stronger left ventricle, are brought together and compressed. Above the apices of the papillary muscles there is left a small chamber around each auriculoventricular valve, which even in the completest contraction is never entirely emptied. The more recent studies of the electric reactions of the heart show that the contraction begins at the base and travels down toward the apex, and, as already noted, it affects the papillary muscles at a comparatively late period. But, also, with Krehl, we are led to recognize a third section of the muscle, the ring musculature, controlling the orifice of the ventricles. This is held to play an important part in preventing regurgitation. Where its tonus is reduced and becomes enfeebled the enlargement of the auriculoventricular orifice leads to incompetence. In the right heart also we have to distinguish a conus or passage leading up to the pulmonary artery. Embryologically this originates as a separate portion of the ventricular cavity. Lastly, it has to be recalled that the weaker right ventricle is applied in a somewhat crescentic manner upon the side of the more conical left ventricle, and that the musculature of the two ventricles is not absolutely distinct. A considerable number of the more superficial fibres pass from the one ventricle to the other. Some clinical observers have recorded an independent rate of contraction of the two hearts. From anatomical considerations it is difficult to see how this can occur.

While the cardiac muscle presents certain distinctive features in its mode of contraction, we must regard it in most respects as possessing the same general properties as other striated muscle. If we attach a weight to a resting band of muscle, such as that of the frog's leg, we find that the band undergoes progressive elongation. So, similarly, if under pressure increasing volumes of blood enter the ventricles, the ventricle expands and undergoes **distension.** It is very probable that, as with skeletal muscle, there is a certain optimum load under which the maximum amount of work is accomplished, and that thus a moderate grade of distension of the ventricles is most favorable for the heart work. Without entering into the physics of the matter we would here point out that with increased exercise up to a certain point the ventricles of the heart undergo a physiological distension, which seems to be to their advantage, inasmuch as in this state a smaller range of contraction of the individual muscle fibres drives out a relatively much larger amount of blood into the arteries. Saying this, it must be remembered that the normal heart possesses a very large reserve of force. It is found, for example, that with the internal pressure raised to four times the normal, the organ still continues to pump out regularly into the aorta. Thus it can stand temporary increase of work with comparative ease. Nevertheless, this reserve of force can be used up either by malnutrition or by continued work up to the limit of the capacity of the·

organ. Where this is the case we find that the organ undergoes what now we may term "pathological dilatation." Even in this dilatation, judging from the continued strength of the pulse and the arterial blood pressure, the organ may continue to function adequately, and drive forward the amount of blood necessary for the organism at large, but this only so long as the individual is at rest. Relatively slight exertion, or increased demand upon the organ brings about cardiac failure and acute distress, or otherwise we recognize three grades—physiological distension, pathological dilatation with partial incompetence, and cardiac failure.

It is probable that in all cases of what we have termed "pathological dilatation" there is incompetence to the extent that regurgitation shows itself. As already pointed out, such regurgitation through the dilated auriculoventricular orifices is of the nature of a safety valve action, whereby the strain is removed from the ventricular muscle at the possibly lesser expense of congestion of the lungs and abdominal and other organs.

So long as the heart is working within the limits of its reserve force we find, in accordance with the principle laid down on page 302, that increased work leads to hypertrophy. When, therefore, we encounter the condition of marked increase in the volume of the ventricular muscle, we must not regard this in itself as a pathological condition. It is adaptive, but, at the same time, is an indication of the existence of some condition, either in the heart itself, as from disease of the valves and obstruction to the onflow of the blood, or outside the heart, whether in the form of obstructive disease of the lungs or of obstruction to the onflow through the systemic arteries. It is an indication that we have to seek for the cause of the increased work upon the heart, either within the organ itself or outside it.

Systole and Diastole.—That systole, the contraction of the cardiac muscle, is an active process is obvious. It is less generally recognized that diastole is likewise active. While this has been suggested by several observers, and while the very firmness and resistance offered to pressure when the beating heart is taken between finger and thumb, is in itself opposed to the view that the diastolic filling of the ventricles is a passive process, it is only comparatively recently that Stefani has afforded absolute demonstration of the active elongation of the heart muscle. He has demonstrated that blood enters the ventricles, and is propelled into the auricles when the pericardial pressure (the pressure acting on the heart walls) is 25 cm. of water higher than that in the venæ cavæ. Only by the suction action of the ventricles, by their active dilatation, can there be continuance of the circulation under these conditions.

These observations throw light upon the hypertrophy of the left ventricle not infrequently present in cases of mitral stenosis; they suggest that the ventricle undergoes increased work in diastolic suction of blood through the narrow orifice. It appears that under usual conditions,

when there is no resistance to inflow, the free entry of blood into the ventricles prevents any pronounced negative pressure in these cavities, so that intraventricular pressure curves often show little or no indication of this phase of active expansion. By analogy we must suppose that the muscular walls of the arteries possess likewise these two properties, and that dilatation under the action of vasodilators is as much an active process as is constriction under the vasoconstrictors.

The Semilunar Valves.—These guarding each a smaller orifice do not need the accessory structures present in the auriculoventricular valves. The cusps close securely, owing to the relatively large extent of the peripheral portions of each of them which comes into apposition with its neighbor, and in this relationship it is interesting to note that acute disease does not affect the cusps along their edges, but immediately below, at the zone of apposition, where appears to be the region of greatest strain.

From the point of view of the work of the heart, the relationship of the aortic valve to the coronaries is of considerable importance. The older view that when open the cusps occlude the coronary orifices, is now known to be wrong. There is a free entrance of blood into these vessels, both during systole and during diastole. Thanks to the existence of the sinuses of Valsalva, there is at all periods a space between the upper aspect of the cusps and the aortic wall.

The Coronary Circulation.—As above stated, blood enters the coronaries during systole. There is, however, no doubt that with the contraction of the ventricular muscle, the intramuscular branches of the coronaries undergo compression, and the heart muscle is comparatively bloodless, compared, that is, with its condition during diastole. It is during this latter and longer period that the main nourishment of the heart fibres occurs.

A study of sections where there has been extensive destruction of the ventricular muscle, through malnutrition, shows that there is a zone or layer of this muscle under the endocardium which still survives. Clearly, therefore, there is in the mammal, as is the case to a much greater extent in cold-blooded animals, a certain amount of nourishment of the myocardium from the ventricular chambers.

To the relationship of the different branches of the coronary arteries to each other we have already referred in discussing the subject of infarcts (p. 424). We would only recall that anastomoses occur, but they are small and infrequent. As shown by Kronecker, ligature of certain of the main branches, particularly of the left side, may be followed in a few minutes by fibrillation of the whole heart, with resultant death. This does not, it is true, occur always, but possibly throws light upon sudden death in some cases of **angina pectoris**, a condition which is especially associated with obstructive disease of the coronary arteries. For the supervention of an attack of angina, it does not seem necessary that there be complete obliterative spasm or other form of closure of the left coronary or its branches. There must, however,

be some narrowing or rigidity of these arteries by disease, so that a call for increased work cannot be met by dilatation and increased nutrition of the heart muscle. The symptoms, that is, of angina pectoris, are those of a relative anemia of the ventricular muscle, or of some area of the same.

The Nervous Mechanism.—It is in this connection that during recent years there has been the greatest advance in our knowledge.

The Intrinsic Apparatus.—1. If the cat's heart, for example, be removed *in toto* and, with as little delay as possible, be perfused with defibrinated blood under proper conditions, the organ will begin to beat and continue to contract actively and with regularity for an hour or more. It is clear, therefore, that there is a mechanism by which auriculoventricular contractions proceed regularly and periodically in the absence of central stimulation.

2. Even with separated strips of mammalian ventricular muscle (Porter), if defibrinated blood be perfused through the attached branch of the coronary artery spontaneous contractions or beats will, under favorable conditions, show themselves. It is clear, therefore, that the contractions of individual fibres may occur in the absence of any stimuli from localized ganglionic centres, situated in the heart.

3. It is still a matter of debate as to whether this last order of contraction is idiomuscular, and this because it seems impossible to isolate any part of the heart musculature which does not show fine nerve fibrils, associated with which are scattered nerve cells.

4. Those who hold to the idiomuscular hypothesis point out that in the chick and other embryos the heart is developed and actively beating *for some days before any nerve fibres and cells reach it from the central nervous system.* There is no question, therefore, that the embryonic heart tissue possesses the power of spontaneous contraction. But in development, as pointed out by Gaskell, this embryonic tissue is replaced by the heart muscle proper. The striking point is that a portion of this primitive cardiac muscle remains and constitutes a very remarkable conduction system, which, evidently, under normal conditions, initiates and regulates the contractions of the organ as a whole.

5. *Conduction System.*—Our knowledge of this system is based upon the observations of Gaskell (1883), Kent (1892), His, Jr. (1893), Tawara and Aschoff (1906), Keith and Fleck (1907), with abundant confirmatory observations by more recent workers. At the junction of the superior vena cava with the right auricle is an accumulation of peculiar small muscle fibres, fusiform with well-marked nuclei, having a plexiform arrangement, and embedded in a densely packed connective tissue. Strands of similar cells pass from this so-called **sino-auricular node** over the inner aspect of the auricular wall and appear to be directly connected with a second node, the **auriculoventricular node**, situated in the neighborhood of the coronary sinus at the base of the auricular septum. From this there passes forward and to the left a bundle of cells of similar nature (the "**bundle of His**"), ensheathed in a fibrous canal, which at the *pars*

membranacea septi of the ventricle divides, the one branch becoming contributed to the left, the other to the right ventricle. Each branch gives off frequent divisions running under the endocardium, the main arborizations being contributed to the papillary muscles of either ventricle, and, further, becoming directly continuous with the subendocardial network of **Purkinje cells**, which lines the interior of both ventricles. These cells have been known for long, and had hitherto been regarded as immature or embryonic muscle fibres. It is through these that the network comes into direct communication with the ventricular muscle proper.

Fig. 227

Model showing the auriculoventricular bundle and its branches. The arrow indicates the left branch. The inset shows the surface of the heart beneath which the bundle runs, from which the endocardium is stripped to show the bundle. (Fahr.)

6. It should be added that associated with this system is an abundant plexus of fine nerve fibrils with occasional ganglion cells, and that the sino-auricular node receives branches, both from the vagus and the sympathetic (accelerator) nerves.

The great importance of this system lies in this, that practically all recent work demonstrates that the regular contractions of the heart are intimately associated with its presence and functional integrity. The recent studies with the electrocardiograph show that the wave of contraction begins at the sino-auricular node. (1) Remove the node and the contractions cease. (2) Destroy the auriculoventricular node and coördination between auricles and ventricles comes to an end. The auricles continue beating at the regular rate; the ventricles at first quiescent, slowly assume a rhythm of their own (the idioventricular

rhythm), the rate of which is roughly one-half to one-third of that of the auricles.

Our present conception of normal cardiac activity is that recurrent periodic stimuli proceed from the sino-auricular node which lead first to a contraction of the auricles, and following upon this, as the wave extends down the auriculoventricular bundle, the ventricles in their turn undergo contraction. And we regard the rate, and, to some extent, the force of the successive waves as influenced by afferent vagus and accelerator influences reaching the sino-auricular node. We recognize further, that these modifications in the heart work are set up by influences acting upon the vagus and accelerator centres of the bulb, whether direct through the influence of circulating blood upon those centres, or reflex, either from stimuli reaching those centres from other organs or parts of the body, or from the heart itself. But, in addition, we recog-

Fig. 228
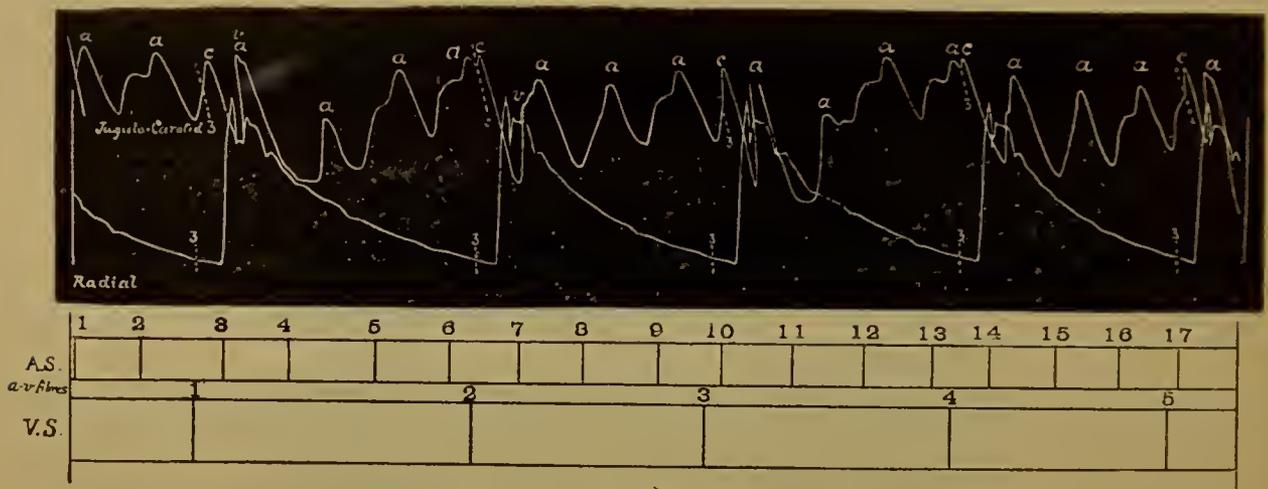
Simultaneous tracings of the jugulocarotid and radial pulse waves. The diagram, constructed from the events recorded in the tracings, shows that no stimulus passes along the *a-v* fibres to the ventricles, but that there is complete dissociation of the ventricular rhythm (*V. S.*) from the auricular (*A. S.*). (Gibson and Ritchie.)

nize that by direct stimulus from within the heart itself, and wholly apart from this conductive system, there may arise a series of independent contractions, whether of the auricular or of the ventricular muscle. The outcome of these investigations has resulted in a mass of observations more particularly upon the various phases and forms of cardiac irregularity, observations so recent that much has still to be clarified, but nevertheless, certain points stand out clearly.

Heart Block.—Just as experimentally it is possible, by injury to the auriculoventricular node and its branches, to bring about incoördination between auricles and ventricles, so a like incoördination is found by clinical and autopsy studies to result from destructive disease affecting the node and bundle. The condition has been known for some years. Numerous cases have been described in which, often suddenly, the pulse had fallen from the normal 70 or 80 to 30 or less, the fall being

accompanied by symptoms of an epileptic type (Stokes-Adams syndrome). It is ingeniously suggested that Napoleon's "epileptic" attacks, in view of his habitual pulse rate of 40 or 50, were manifestations of this disease. In many cases this bradycardia or slow beat has persisted for years. Other cases have been noted in which the condition comes in paroxysms. The more recent employment of phlebographs, with record of the venous pulse, has shown that in these cases, while the ventricles are slowed, the auricles retain their normal rate. The various grades of this heart block may show themselves either as (1) a lengthening in the interval between the onset of auricular and ventricular systoles, (2) an occasional ventricular dropped beat, (3) periodic dropped beats, every tenth or ninth pulse, etc., being wanting, until there may be developed a condition known as two-one rhythm, or three-one rhythm, the auricles beating twice or three times the rate of the ventricles, or, lastly, complete heart block, so that there is no relationship between the two rhythms. Here, with entire failure of transmission, the ventricles may beat for years with an inherent or idioventricular rhythm.

Other Forms of Arrhythmia.—The time is not yet ripe for a complete classification of the arrhythmias. Some of these are clearly of external or nervous origin. Thus, in those recovering from acute illnesses, there may be marked changes of pulse rate which clearly are associated with the respiratory act. These appear to be of vagus origin. Experimentally it can be shown that vagus stimulation either may bring the heart to a standstill, may slow the heart rate, or may so act upon the conduction apparatus as to arrest the passage of auricular impulses to the ventricle. But others are associated with conditions in the heart itself, and due to some form of irritation. While the heart muscle is insensitive to any stimulus reaching it during the period of contraction, it responds to stimuli reaching it in the diastolic phase. We thus may come across regularly or irregularly interposed beats unrelated to the regular rhythm. These beats may be interposed in the ventricle alone, or in the auricle alone, or in both.

Fibrillation.—What may be regarded as the extreme condition of irregularly interposed beats is the condition of fibrillation or **delirium cordis.** In this, instead of a wave passing regularly through the heart muscle, different areas of the muscle are seen to be contracting independently, so that there is no contraction of the heart as a whole, but the organ passes into a condition of progressively increasing dilatation, with an extraordinary fibrillary movement of the whole surface— appearances such as might be given by a mass of small worms, densely packed, wriggling actively in a thin-walled bag. Where this condition affects the ventricles, unless it be immediately arrested by vagus or other action, the result is death, and that because the circulation is inevitably arrested. It seems probable that this ventricular fibrillation is a cause of sudden death in some conditions of long-continued and grave cardiac irregularities. One of the most interesting of recent observations on the heart is that in cases of obstructive cardiac disease

there may be dilatation and fibrillation of the *auricles*, persisting for months, if not for years. Both by study of the venous pulse and by the cardiograms, this fact is now well established. It is but another confirmation of the point made at the beginning of this chapter, that from the point of view of the pumping action of the heart, the auricles are not essential, but simply serve as reservoirs.[1]

THE PERICARDIUM

From this point on we shall in due order pass in review the main features of the morbid anatomy and histology of the different organs. It would be well to say here a word or two regarding the system employed. A definite order will be preserved in connection with each section, the treatment being as follows:

(1) *Abnormalities*, (2) *Circulatory Disturbances*, (3) *Inflammations*, (4) *Regressive Disturbances* (degenerations, infiltrations, necroses, traumatic disturbances), (5) *Progressive Disturbances*, including new growths, (6) *Any conditions not coming under the above headings*. It will be understood that where any one of these headings is passed over, no disturbance of this particular order is deemed noteworthy in connection with the organ under consideration.

In the second place, not merely for economy of space, but also as a due mental exercise, it is taken for granted that the reader is familiar with the main morbid processes. Thus, for example, in noting the existence of diphtheritic or catarrhal inflammation of a given surface, it is not thought necessary to enter into a detailed description of these types of inflammation; at most, any departure from the ordinary type will be noted, together with any peculiarities in the gross appearance of the affected parts.

And, lastly, it must be clearly understood that the treatment is not intended to be exhaustive. Our object is to pass in review these conditions with which the ordinary, as distinct from the advanced, student ought to be familiar.

With these prefatory remarks we now pass on to the pathological and histological anatomy of the pericardium.

Abnormalities.—There is only one noteworthy abnormality of the pericardium, and this is rare, namely, the condition of defect, either partial or complete, of the parietal layer, resulting in either a passage or communication between the pericardial and left pleural sacs, or in the heart lying, as it were, naked, in apposition to the left lung.

Circulatory Disturbances.—All serous surfaces, from the similarity in their structure, show a similar succession of changes associated with

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[1] A late work upon these subjects is by Thomas Lewis, "The Mechanism of the Heart Beat," London: Shaw & Sons, 1911. Articles upon the same subjects are to be found in both Allbutt's and Osler and McCrae's Systems. The classical work upon the venous pulse is that of J. Mackenzie, "A Study of the Pulse," 1902. Of equal importance is his "Diseases of the Heart," London, 1908.

different grades of circulatory and inflammatory disorders. The abundant network of capillaries situated immediately underneath the endothelial layer renders them all peculiarly liable to present profound change. Thus, in the first place, at post mortem we frequently encounter pericardial **petechiæ**, due apparently to irregular and spasmodic heart action in the agonal period, with consequent distension and rupture of some of the poorly supported superficial capillaries. The hinder aspect of the heart is a not infrequent seat of these petechiæ. Certain toxic substances, phosphorus, and the like, are peculiarly apt to lead to these multiple small hemorrhages, secondary, it would appear, to degeneration of the capillary endothelium. They may appear, that is, not only in the agonal period, but also during the course of acute intoxications and infections.

Hydropericardium.—Of more importance is hydropericardium, with accumulation of serous fluid in the pericardial sac. This serous cavity differs from the others in that normally there is present a small accumulation of serous fluid (from 10 to 20 c.c.). In obstructive heart disease the amount becomes greatly increased (from 100 to as much as 1000 c.c.) An interesting point is that, despite this large amount of fluid, and the pressure it brings to bear upon the heart, there may be this extensive accumulation of fluid without arrest of the heart action. With the gradual pouring-out of the fluid there is expansion of the parietal pericardial sac, so that the pressure does not rise sufficiently high to compress the auricles, and so arrest the onflow of blood. This condition of hydropericardium is the result of obstructive heart and lung disease, and, as such, is associated with the transudation of fluid into the other cavities of the body. It is significant that there is no constant relationship between the extent of the accumulation in the pericardial, pleural, and peritoneal cavities; there is considerable variation in the relative amounts.

Hematopericardium.—Hematopericardium results (1) from extreme dilatation of the pericardial capillaries, with hemorrhage from the same, (2) from trauma, (3) from rupture of the heart, or (4) rupture of the first part of the aorta, either from a simple or from a dissecting aneurysm. In the first of these cases there is a combination of hydro- and hematopericardium, and the condition is not necessarily fatal. In the last two the sudden outpouring of blood into the pericardial cavity prevents gradual and adaptive expansion of the parietal pericardium, and the pressure may become so great that the accumulation of blood is in itself the cause of death by arresting heart action.

Anemia.—Anemia of the pericardium coexists with anemia of other organs.

Inflammation.—Pericarditis.—The first stage of an acute inflammation of the pericardium is characterized by an intense congestion of the superficial vessels, with erosion and destruction of the endothelium, followed by slight formation of fibrin on the surface. This stage in which there has so far not been much fluid exudation, is characterized

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clinically by the presence of friction sounds or rubs, the roughened surfaces of the epicardium and parietal pericardium rubbing one against the other. It is rare for this dry form to continue more than a few hours; more frequently it gives place to a *serofibrinous* pericarditis, with disappearance of the friction sounds. In this form there becomes developed a layer of fibrin on both the pericardial surfaces, which sometimes assumes a great thickness, and through the constant movement of the heart and the eddying of the fluid exudate, instead of being smooth the fibrinous layer is ridged or even shaggy and villous, assuming often a characteristic "bread-and-butter" appearance, *i. e.*, that of the butter between two slices of bread when those slices have been quickly pulled apart. Fibrin so deposited can easily be scraped off the surface of the heart with a knife-blade or finger nail, exposing the reddened underlying pericardium. According to relative abundance of the fibrin formation and fluid exudate, so do we speak of either a *serofibrinous* or a *serous* pericarditis. In some early acute cases, as also in the acuter cases of tuberculosis of the pericardium, the congestion is so extreme that in place of a simple serous exudate there is a hemorrhagic inflammation.

Fig. 229
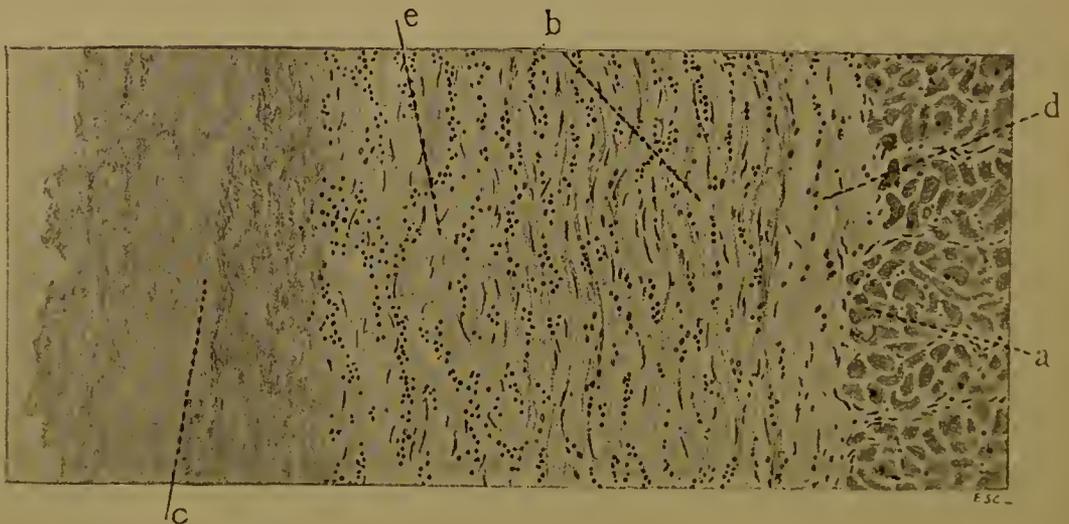
Section from case of recurrent pericarditis: *a*, myocardium; *b*, *e*, layers of connective tissue, the result of previous attacks of inflammation; *c*, deposit of fibrin, the result of recent acute inflammation; *d*, the limit of the normal connective-tissue layer of the pericardium.

Serous pericarditis is seen in cases of acute rheumatism, chronic nephritis, and other conditions in which the indications are that we deal with infection and bacteriemia, due to organisms of low virulence, or again, it may be due to intoxication. Here, also, may be included a somewhat rare form associated with the extension of malignant growth to the pericardium.

Purulent Pericarditis.—This form is, in general, set up by the pyococcus, streptococcus, or pneumococcus, although occasionally other microörganisms of acute infection are found as the causative agents. Here, with the excessive pouring out of leukocytes there is a coincident

proteolytic digestion of any fibrin that has been formed. The pericardial cavity is found filled with thick pus.

Chronic Pericarditis.—An acute fibrinous pericarditis may, if of only moderate extent, undergo complete resolution, with complete absorption of the fibrin. If, however, the deposit be at all extensive, either this absorption is not universal or is largely wanting, and in its place organization ensues, with the passage of new capillary vessels into the fibrinous layers, and replacement of the fibrin by new connective tissue. While in the acute stage the opposed layers of fibrin are separated by serum, in the process of healing the excessive fluid becomes absorbed, and thus the now apposed layers come into contact and become adherent, and as the process of organization continues there is first vascular and then connective-tissue connection between the epicardial and the parietal layers. In this way there are developed *adhesions* which may be either (a) localized, as, for example, in the region of the apex, and then in the form of fibrous bands, or (b) generalized over both ventricles, or (c) universal, resulting in what is known as **synechia** or adherent pericardium. This process of organization takes days if not weeks to become complete, and such fibrosing continuation of an acute attack is **simple chronic pericarditis.** But once formed these organized adhesions are apt to be permanent; at autopsy we encounter *not a true chronic pericarditis,* but an *old* condition of **pericardial adhesions.** When the heart is thus adherent to its surroundings, it will be obvious that the organ in contracting has, as it were, to drag with it the chest wall; its work is thus greatly increased, and dilatation and hypertrophy quickly follow. This work is much lessened if the bony and cartilaginous parts of the chest wall over the heart be removed by operation.

It is not infrequent to meet with a condition of acute pericarditis implanted upon a thickened fibrous pericardium, the results of previous inflammation. This **recurrent pericarditis** may be met with in recurrent acute rheumatism; not infrequently, however careful examination will show that we deal with a tuberculous affection. While we may encounter the more acute form of tuberculosis of the pericardium, with abundant recognizable tubercles throughout the thickened pericardium, it is frequent, in cases of tuberculosis, to find few tubercles or caseous areas proper, but, in the main, a diffuse extensive connective-tissue formation, the fibrous tissue being laid down in regular layers, which, toward the free surface, give place to a recent fibrinous pericarditis (see Fig. 229).

Syphilitic Pericarditis.—This form is not frequent. It appears generally as a continuation or extension of syphilis of the heart muscle with formation of adhesions. Actinomycosis is as rare or rarer. Here may be noted the condition of **indurative mediastinopericarditis,** a condition in which the inflammation of chronic type with adhesions extends into the surrounding mediastinal tissue and pleura, and, with the contraction of the tissue, is apt to pull upon and distort the heart, giving rise to aberrant murmurs and paradoxical pulse.

"Milk Spots."—To this category also belong milk spots. These are localized patches of thickening of the epicardium seen most frequently upon the front of the right ventricle; they may be present also at the back of the ventricles, and less commonly over the auricles. They are slight overgrowths from hypertrophy of the epicardial connective tissue, and appear to be induced by the rubbing of the heart wall against the parietal pericardium in cases of dilatation of one or other cavity.

ETIOLOGY.—A word or two may be said regarding the causation of pericarditis. It appears probable that there is no such thing as true primary idiopathic pericarditis. The organism setting up the inflammation must reach the part from some focus elsewhere. Cases are either of *hematogenous* origin, the infective agent being brought by the blood, or, more frequently, derived *by extension*, and secondary to inflammation either of the heart muscle, of the pleura, or the diaphragm. Pericarditis, in fact, is a fairly common accompaniment of pneumonia. As already indicated, a great number of species of organisms may be isolated from instances of one or other type. It deserves note that tuberculous pericarditis is found, upon careful examination, to be more common than the naked eye apearances would suggest. Lastly, the frequency of pericarditis in elderly individuals, victims of chronic nephritis, deserves mention. The conditions here are generally of the serous type, and frequently on bacteriological examination the results are negative. Whether we deal with a toxic pericarditis, or, as appears to be the case also in acute rheumatism, the causative agents are such as do not grow easily upon the ordinary media, is a matter which has still to be determined.

Regressive Disturbances. — Of these only one condition deserves note, namely, that of **serous atrophy** of the pericardial fat. In senile conditions, as also following exhausting diseases, the fat of the fat cells may become replaced by serous fluid, so that without much shrinkage, the regions where fat has been, in the auriculoventricular groove, etc., assume a translucent, soft, gelatinous appearance.

Progressive Changes.—**New Growths.**—Primary neoplasms are rare, and are of sarcomatous type or endotheliomatous. Nor are secondary growths very common, though these may occur by extension, as, for example, in cases of mediastinal **lymphosarcoma**, or by metastasis.

Cases of **cysticercus** and **echinococcus** hydatids have been described.

MYOCARDIUM

Abnormalities.—Abnormalities of the heart are not uncommon, most often due to defective development, occasionally the results of intra-uterine disease. They affect mainly the myocardium, but the valves and larger vessels may be involved. It is simpler to consider

them all as a group. Saying this, it has to be admitted also that they are so various that only the more important can be touched upon.[1]

We may divide them into four main groups: (1) those affecting the heart as a whole; (2) those due to imperfection in the development of the septa which convert the original two-chambered heart into four chambers; (3) those due to imperfection in the development of the systemic and pulmonary arteries out of the original single efferent trunk; and (4) abnormalities of the main venous and main arterial trunks, ductus arteriosus, etc.

1. Under the abnormalities of the heart as a whole are to be included **displacements, duplication, hypoplasia,** and primary congenital **hypertrophy.** The heart has been found to assume a transverse or vertical instead of an oblique position, or to be **dislocated,** so as to be high up in the neck, even at the level of the base of the tongue, or, through defect of the diaphragm, in the abdominal cavity, or through defect of the sternum, to be exposed to the exterior (**ectopia**). Or, again, it may be **transposed,** lying in the right thorax, in which case in general, though not always, there is found transposition of other viscera. A case in which there were seven functional hearts in series has been recorded in the chick. **Hypoplasia** of various grades is found down to complete absence in acardiac monsters. Primary congenital hypertrophy, in which the weight of the organ may be more than twice the normal, has been recorded by a few observers, the causation being unknown.

2. *Imperfect development of septa* may affect (*a*) the interauricular septum, (*b*) the interventricular septum, and (*c*) both septa. The **interauricular septum** has a double origin, two primary septa growing downward, and lying obliquely; between these is the channel of communication between the auricles, which is patent until birth, conveying the blood from the inferior vena cava across to the left heart. It frequently remains patent in post uterine life. This patency of the foramen ovale is the commonest of all abnormalities of any organ. In Montreal we have found it thus patent in 14.5 per cent. of our autopsies, and believe this to be an understatement, as frequently the oblique channel is so small as only to admit a fine probe. At other times it is large and conspicuous, there being various grades up to complete absence of septal development, up to the condition of **cor biventriculare triloculare,** with a single auricular cavity. Often this condition is accompanied by no physical signs or symptoms, but aberrant murmurs have been recorded, together with the development of cyanosis when the pulmonary circulation has become obstructed.

The **interventricular septum** develops from below upward, and here again various grades of defect are on record, from total absence (**cor biatriatum triloculare**) down to a minute orifice in what is known as the "undefended space" in the upper portion of the ventricles imme-

[1] The most comprehensive study in our language is to be found in the article of Dr. Maude E. Abbott in Osler and McCrae's Modern Medicine, vol. iv, 2d ed., 1914.

diately beneath the semilunar valves. The indications are that in these cases the current is from the stronger left ventricle into the right, with secondary hypertrophy of the right ventricle. Here again there may or may not be cyanosis, and the development of a systolic murmur heard to the left of the sternum about the third space.

Both in the auricles and in the ventricles are found occasionally **accessory imperfect septa.**

3. Originally there is a single primitive arterial trunk which in very early embryonic life becomes divided into two great vessels by the development of a septum. There may be (*a*) complete absence of development of this septum (**persistent truncus arteriosus**), this common vessel giving off the pulmonary vessels and continuing as the aorta. (*b*) The commonest abnormality is **deviation of the septum,** so that we obtain various grades of irregularity in the origin of the aorta and pulmonary artery up to conditions in which the aorta originates from the right ventricle, the pulmonary artery from the left. Or (*c*) the septum leads to an unequal division of the trunk, so that one artery, most commonly the pulmonary, is minute or obliterated (**congenital pulmonary stenosis with atresia**); rarely the origin of the aorta shows the same character. These conditions may be produced either by mere vice of development, or by intra-uterine inflammation. In pulmonary stenosis compensation is obtained by persistence of the widely **patent ductus Botalli** (or **d. arteriosus**). There may also be dilated bronchial arteries aiding the pulmonary circulation. It is these cases of pulmonary stenosis that present the characteristic picture of congenital cyanosis (**morbus cæruleus**).

Intimately associated with defects in development of the aortic septum are abnormalities of the pulmonary and aortic semilunar cusps. These cusps originate as four endocardial cushions, two of which become subdivided in the descent of the arterial septum, so that normally six cusps are developed, three in each artery. There may be increase in number, such supernumerary cusps being more frequent in the pulmonary artery, or, on the other hand, decrease, a bicuspid condition of the pulmonary, or again of the aortic valve being occasionally recorded. The latter condition must be distinguished from fusion of the cusps, the result of postnatal inflammation.

4. To our fourth group belongs a variety of conditions, such as patency and abnormalities of the ductus arteriosus, coarctation of the aorta, hypoplasia of the aorta, anomalies of the aortic arch, of the coronary arteries, of the systemic veins, and of the pulmonary veins. During foetal life the ductus arteriosus joining the pulmonary artery and aorta is a short, thick trunk, 12 mm. long, passing from the region of the bifurcation of the pulmonary artery to the under side of the arch of the aorta, below the origin of the left subclavian. It carries the blood, which reaches the right ventricle from the head and upper extremities, from the pulmonary artery into the descending aorta. At birth the pulmonary blood becomes diverted into the lungs and the

ductus undergoes rapid involution, with, normally, complete obliter-ation in the third week after birth. Occasionally (1) it remains patent, or again (2) can undergo aneurysmal dilatation, or (3) very rarely it is completely absent, in which case may be found defect of the inter-ventricular septum, or (4) it may present an anomalous course. **Coarcta-tion of the aorta** is the name given to narrowing or stenosis of the descend-ing arch immediately above the insertion of the ductus arteriosus. The arch, it may be pointed out, is little used during fœtal life, and this stenosis is the result of a failure of the aorta to dilate and adapt itself to the altered conditions of circulation at birth. As a result the blood from the left ventricle reaches the trunk and lower extremities through an extraordinary series of anastomotic vessels (as shown in Fig. 222).

Circulatory Disturbances.—Of these the most striking is the series of disturbances which may result from **obstruction** of one of the coronary arteries or its branches, more particularly of the left coronary. From the fact that the coronary vessels originate at right angles to the aorta, **embolism** is rare, although we have encountered one case and have heard of another in which the mouth of the left coronary has been found obstructed by a thrombus forming in the underlying pocket of the aortic valve. Localized **thrombosis** is the more common event, most often secondary to chronic endarteritis (arteriosclerosis). The results are variable; (1) if the branch be small little harm ensues. There may be sufficient collateral circulation. (2) If larger, the area of supply undergoes necrosis and infarct formation. The early stage of this is, without reason, termed **myomalacia.** There are the usual characters of a red infarct with hemorrhagic congestion and death of the muscle fibres. Such necrosis may be followed by either (*a*) rupture, (*b*) giving way of the damaged heart wall, with formation of ventricular aneurysm, or (*c*) healing and fibrosis, or cicatrization. Malnutrition of the heart muscle from either complete obliteration of a branch or branches of the coronary artery, or from narrowing of the same and relative anemia, appears to be the most common cause of cardiac **fibrosis**, or, as it is usual to term it, "**interstitial myocarditis.**"

Œdema, passive congestion, and hemorrhages may all be met in the myocardium.

Inflammation.—Acute myocarditis is possibly more common than is usually supposed. From its very activity the myocardium is pecu-liarly susceptible to toxic agents circulating in the blood; the cloudy swelling, often going to fatty degeneration, encountered in the different acute fevers, may be regarded as the result of diffuse irritation and so as an **acute myocarditis.** But beyond this we may encounter a more obvious inflammation with small-celled infiltration in pyococcus and streptococcus infections, and in acute rheumatism there is a rather characteristic form of myocarditis, to which Aschoff has called atten-tion, in the form of localized nodes of small-celled infiltration along the course of the vessels; in some cases of ulcerative endocarditis, due to pyogenic organisms, there may be isolated or multiple small abscesses

developed in the heart muscle, secondary to small infective emboli.
Acute miliary tuberculosis is rare. Some cases are on record of multiple
syphilomas—minute localized accumulations of small round cells not
very well defined (miliary gummas).

The more chronic forms of tubercular and syphilitic lesions are not
common. Caseous foci have been described, together with solitary
gummas. More common both in tuberculosis and syphilis, and as
the end result of the localized inflammatory lesions due to pyogenic
organisms, is the formation of cicatricial tissue and the development
thus of localized fibroses.

Fig. 230
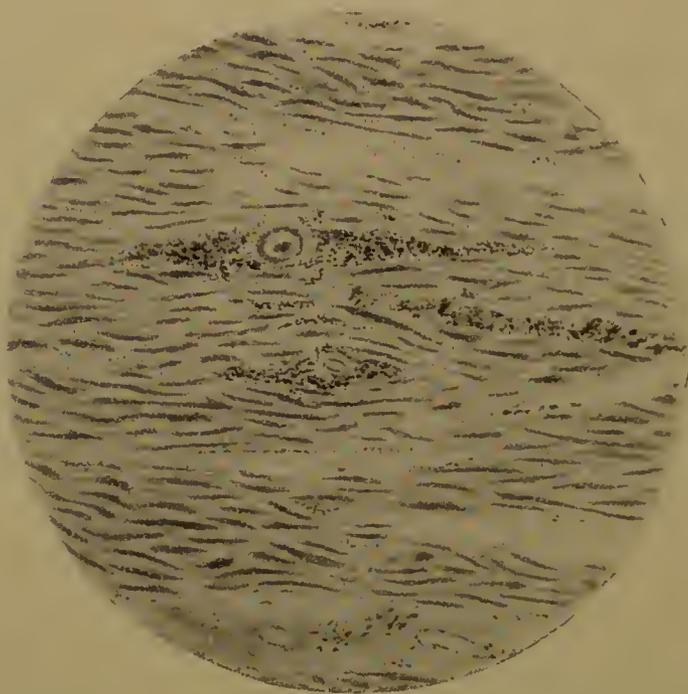
Acute interstitial myocarditis. The dots represent cellular infiltration chiefly around the vessels.
Low power. (Prof. Oskar Klotz.)

Regressive Changes.—The heart muscle is very susceptible to
alterations in nutrition and function and exhibits thus a variety of
regressive disturbances.

Atrophy.—Simple or brown atrophy is very common. In elderly
individuals and in the subjects of progressive wasting disease, the
ventricular muscle is found lessened in amount presenting on section,
a darker, more mahogany-brown color than normal. The microscopic
appearances have already been described (p. 264). In general autopsy
work this is perhaps the commonest of all cardiac disturbances to be
encountered, although the next regressive change to be noted runs
it a close second. (See Plate VII, Fig. 1.)

Cloudy swelling (p. 268) is seen, particularly in cases of hyperpyrexia,
febrile disturbances, and infectious disorders. The ventricular muscle
in these cases no longer presents the normal rich meaty color, but has,
on section, the dull, paler appearance of meat that has been dipped in
boiling water.

Fatty infiltration is not uncommon in the obese and sedentary, and
is found associated with extreme epicardial development of fatty

tissue. Here little collections of fat cells are found lying between the bands of muscle fibres around the vessels. Their presence leads to

FIG. 231

Section of myocardium from case of fatty infiltration: *a*, arteriole cut obliquely; *f, f*, fat cells in connective-tissue surrounding arteriole.

FIG. 232   FIG. 233

Fatty degeneration of papillary muscle. (McGill Path. Mus.)
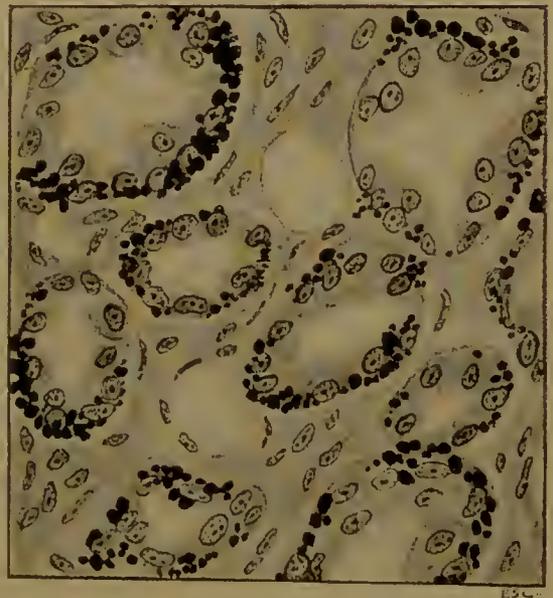
Fatty degeneration of heart-muscle fibres, showing different grades of involvement of the individual fibres; fresh specimen. (Ribbert.)

malnutrition and disturbance of function of the heart muscle. This condition appears to be a frequent cause of the weak heart and cardiac

incompetence of stout individuals. In our experience the right heart tends to be more involved than the left.

Fatty degeneration (p. 270) is also common, either as a diffuse change or in multiple small foci of degeneration alternating with unaltered areas, giving the myocardium a grained appearance and producing what is known as the "**thrush-breast**" heart. This condition is best seen on the naked-eye examination of the interior of the left ventricle, often showing itself well in the papillary muscles. The heart muscle in these cases is shrunken and very friable, so that upon pressure between the fingers and thumb the tissue easily breaks up; sometimes

FIG. 234
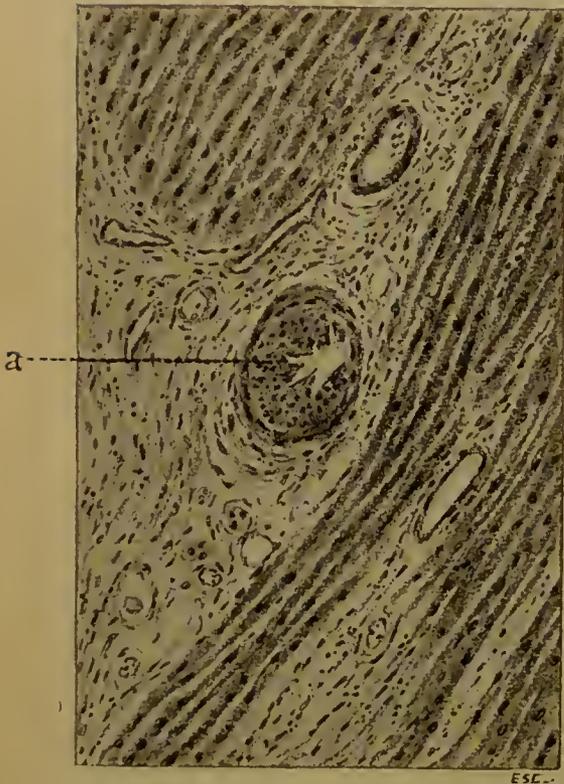
FIG. 235
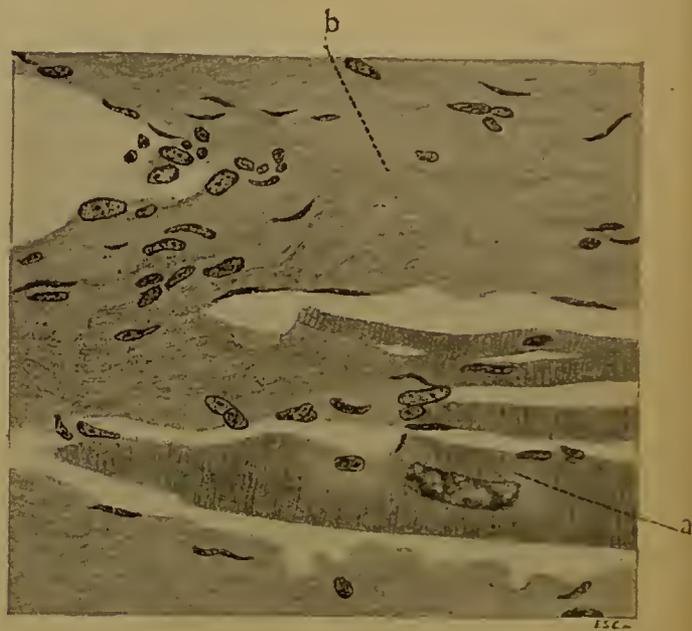
Section of myocardium to show peri-arterial fibrosis: *a*, arteriole with well-marked endarteritis obliterans; other patches of fibrosis to be observed in the lower part of the field.

Sections through edge of developing area of myo-cardial fibrosis showing the cardiac muscle fibres (*a*) merging almost imperceptibly into the hyaline fibroid area (*b*).

indeed it has almost a buttery consistence. In our experience, the diffuse form in which the whole of the muscle has a paler yellowish appearance, is found as a result of extreme toxic conditions, the thrush-breast form in conditions of malnutrition and advanced anemia, notably in cases of pernicious anemia. In the latter form the small areas of degeneration are the parts farthest away from the blood supply, the muscle immediately around the terminal arterioles not being involved.

Amyloid or **chondroid degeneration** is found in the more advanced cases of general amyloidosis, as in long-continued cases of Pott's disease. As elsewhere it shows itself by a deposit of the amyloid material in the middle coats of the arteries and along the capillary network. The so-

called **Zenker's** or **vitreous degeneration**, or hyaline necrosis of individual muscle fibres, is more common than is usually taught. Notably, it is to be found in cases of malnutrition and particularly where there is blocking or obliteration of branches of the coronary artery. Muscle fibres are found swollen and hyaline, with loss of nuclear stain and of striation, exhibiting various stages of replacement by fibrous tissue.

Fragmentation.—In examining sections of the heart muscle it is not unusual to come across abundant fractures, as it may be termed, in the course of the fibres. Around these no reactive change is to be noted, and there has been much discussion as to whether these are artefacts or the result of agonal rupture of the fibres, due, for example, to a terminal state of irregular fibrillary contraction of the ventricles. That it is not a mere artefact we are inclined to think from the fact that the condition is frequent in certain particular conditions, absent in others. Thus, Landry, working in our laboratory at the Royal Victoria Hospital, noted that it was practically constant in cases of aneurysm of the transverse arch of the aorta, associated with more or less fatty degeneration. · Hektoen distinguishes between true fragmentation, in which there is rupture along the course of a fibre, and **segmentation**, occurring along the lines of demarcation between the separate fibres.

Fibrosis.—We shall refer to this more particularly under the heading of Interstitial Myocarditis, noting here that it is a frequent result, not only of acute inflammation, but also of degeneration and necrosis of areas of muscle tissue. Associated with it we frequently get **hyaline** change (p. 276), more rarely we encounter **calcification** (p. 280).

Here, as an outcome of degeneration and necrosis, may be noted the occurrence of **rupture of the heart.** This may follow fatty degeneration or infiltration, but, more frequently, is the outcome of coronary disease, with localized necrosis. The most frequent site is the lowest third of the left ventricle in front. The condition may also follow upon abscess or new growths.

FIG. 236

Wall of left ventricle cut into obliquely, or roughly parallel to the internal aspect, to show extensive areas of fibrosis: *a*, area close under the endocardium; *b*, areas in depth of myocardium. (McGill Pathological Museum.)

Progressive Changes.—Hypertrophy.—Hypertrophy of the muscular elements, both in the auricles and, more markedly, in the ventricles,

is distinctly common. Anything, in fact, which leads to increased work of the heart, or of any single chamber of the heart, within the limits of its reserve force, is followed by overgrowth of the muscle, and this sometimes to an extraordinary extent, so that cases are on record in which the heart, instead of weighing the average 300 grams, has weighed 1900. Usually the condition is one both of simple hypertrophy and of hyperplasia. Not only are the individual fibres of increased size, but their number is increased. We may classify the causes of increased work and so of hypertrophy as follows:

I. Increased load in the form of increased volume of fluid to be propelled, as in true plethora ("Munich beer heart").

II. Increased load, in consequence of obstruction to the onflow of blood:

1. In the peripheral circulation, as in some forms of arteriosclerosis, and chronic Bright's disease.

2. Within the heart itself.

(a) Through valvular stenosis and obstruction, resulting in hypertrophy in the chamber or chambers behind the obstruction.

(b) Through valvular incompetence and regurgitation, the regurgitant blood adding to the load and volume to be expelled out of the chamber receiving it.

III. Increased load, due to hindrance of contraction exerted from without, as by pericardial adhesions.

IV. Increased activity of the heart, due to central nervous stimuli. In the earlier stages of the tachycardia of exophthalmic goitre the heart has been found distinctly hypertrophied. If the cause of the hypertrophy persists, and, as often happens, becomes progressively aggravated, the hypertrophy is apt to give place first to dilatation and then to exhaustion, and in these cases, although the heart is found enlarged and of increased weight, microscopically the individual fibres no longer appear enlarged and hypertrophied. Without taking up the individual cases of hypertrophy of particular chambers we may here lay down the general rule that it is the chamber which bears the brunt of the increased work that first shows hypertrophy. Thus, where there is stenosis of the aortic valve it is the left ventricle, in pulmonary obstruction the right ventricle, that is first hypertrophied. And, in the second place, hindrance to the onflow of blood from one chamber tells secondarily upon the chamber immediately behind, and leads to its hypertrophy. Thus, where there is aortic stenosis, the left auricle in time undergoes hypertrophy because it attempts to empty its blood into an already crowded ventricle, and this is followed in course of time by hypertrophy of the right ventricle.

Dilatation.—Dilatation is not a progressive but rather a regressive condition. In passing, we would recall our contention that two distinct conditions are to be recognized, a physiological distension which always accompanies increased work thrown upon the heart, followed by hypertrophy, and a pathological dilatation, an indication

that the heart cannot fully respond to the work thrown upon it, a condition in which microscopically we find that the fibres which had undergone a true simple hypertrophy now show regressive changes, with some shrinkage.

New Growths.—Primary tumors of the myocardium are distinctly rare, although **fibromas, myxomas,** and **lipomas** have been reported. The most typical primary tumor is the **rhabdomyoma,** a condition generally of multiple tumors found in children and so of congenital nature, which is generally associated with congenital nervous and other disturbances. Secondary growths are not uncommon, **sarcomas** being more frequent than **carcinomas.**

THE ENDOCARDIUM

Endocarditis is so often confined to the valves that when we use this term we are apt to picture to ourselves a "valvulitis" and by association, to forget that the endocardium includes the whole of the lining of all the heart chambers, and that regions other than the valves may be the seat of disturbance.

Abnormalities.—These are rare and confined to the valves. There may be **accessory semilunar valves** or only two; very rarely has been recorded a **double orifice** of the mitral. **Aberrations** of the chordæ tendineæ, and cords passing from one papillary muscle to the other without touching the mitral cusp are not very uncommon. A still more frequent abnormality is **fenestration** of the semilunar valves. These fenestrations are situated immediately beneath the free edge in the area of apposition and cause no functional disturbance.

Circulatory Disturbances.—The circulatory disturbances are of slight importance. The healthy valves are non-vascular, but, just as in the cornea, after inflammation, there is development of the vessels, so here, and with recurrent inflammation there may, though rarely, be **hemorrhages** within the valve substance. In infants minute pinhead **hematomas** are occasionally encountered, generally toward the closing edge of the mitral cusps. The latest view is that in the course of development minute pockets become formed, lined by endothelium, which, becoming covered in by the endothelium above, form closed sacs containing blood. They are not, therefore, associated with the presence of vessels. The bright red color of the endocardium occasionally met with is due to **hemoglobin imbibition,** and is usually a post mortem appearance (p. 289).

Inflammation.—Endocarditis.—The commonest and most important series of disturbances, seen in connection with the endocardium, are usually included under the heading "endocarditis," whether acute or chronic. Acute endocarditis most frequently affects the valves, although it must be remembered that the mural endocardium may also be involved, and that the succession of changes seen more particularly

in connection with the valves, may also be encountered affecting the walls of ventricle or auricle.

There is experimental evidence that the endothelium lining the heart has phagocytic powers and can take up bacteria from the blood. Following Washbourn, we may imagine that at points of narrowing, where the blood stream impinges upon the endocardium, this phagocytic action is most likely to occur, and so the auricular aspect of the auriculoventricular valve and the ventricular aspect of the semilunar valves are areas favorable to this process. But at the same time these are the regions which, from their constant movement, are the subjects of greatest stress, and, as a consequence it may happen that if weakened, these cells, instead of destroying the bacteria taken up, permit the intracellular multiplication of the bacteria and themselves become destroyed, the bacteria in their multiplication involving other cells in the immediate neighborhood. In quite another way, the infection may reach the valves by means of the bacteria carried into the nutrient

Fig. 237   Fig. 238
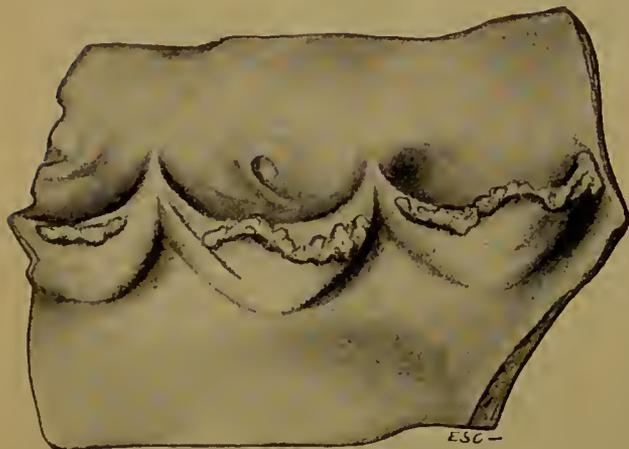
Verrucose endocarditis of aortic valve.   Aortic endocarditis with vegetation (*a*).
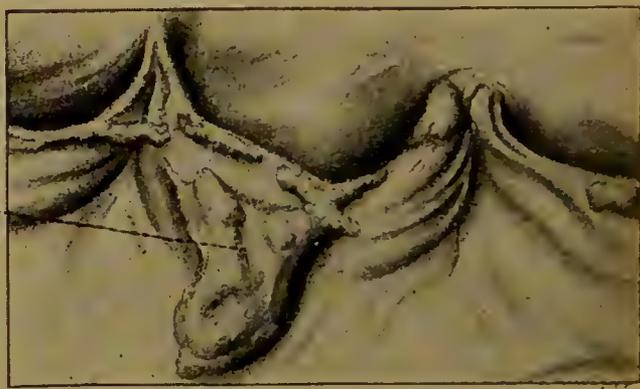
arteries of the valves, these vessels being relatively independent and having but poor anastomosis. Emboli or minute thromboses are formed with resulting poor nutrition and readiness of the valve substance to break down. With destruction of the lining cells there is now developed an area at which thrombosis is favored, and thus what are known as **vegetations** become developed. According to the extent of surface involved, according also to the virulence and properties of the infecting microbe, so do we obtain variation in the extent of these vegetations. If we deal with organisms of mild virulence, with relatively little spread into the surrounding tissue, the vegetations remain small, and there is developed what is known as a **verrucose** endocarditis. If they spread and involve a relatively large area of the endocardium, then a large base is provided for the thrombotic process, and large, almost cauliflower-like vegetations are produced. If, again, the microbes are strongly proteolytic, the fibrin of the vegetations becomes digested, the vegetations with their contained bacteria soften and break off, and, carried

Fig. 239
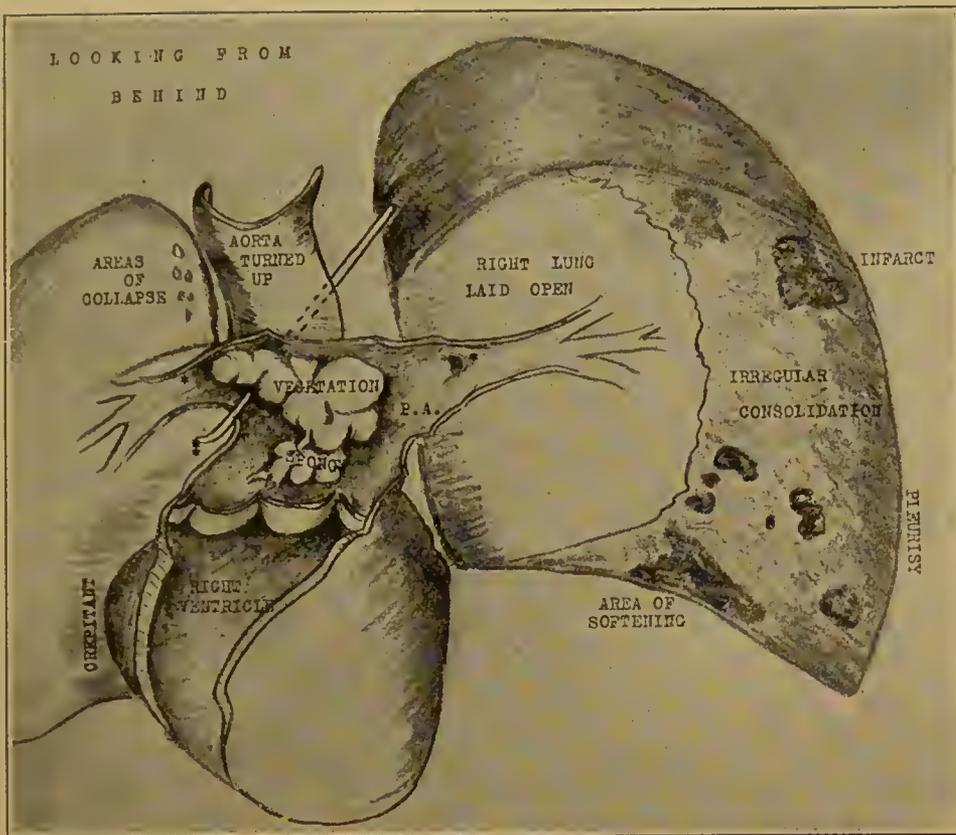
Diagrammatic drawing showing acute vegetative endocarditis of pulmonary artery and the consequent infarcts of the lung; the area surrounding the infarcts and the pleura overlying is the seat of inflammation. The ductus arteriosus remained patent, and a probe is seen passed through it. (W. F. Hamilton.)

Fig. 240
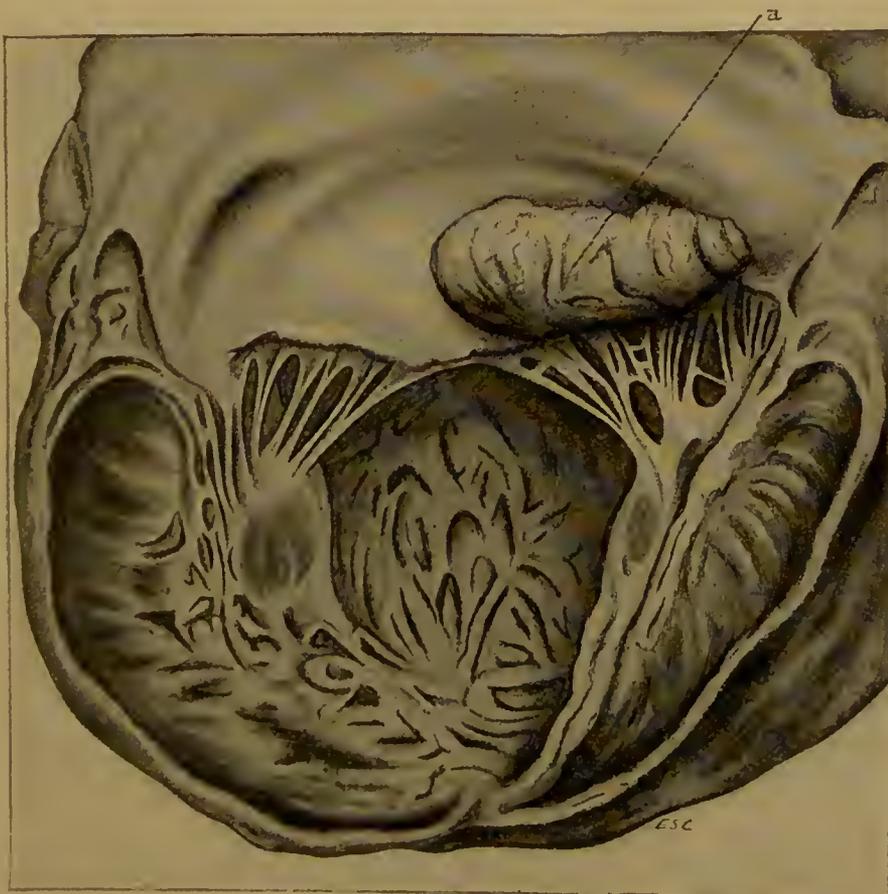
Vegetative endocarditis of mitral valve: vegetation on auricular surface at *a*. (McGill Path. Mus.)

by the blood stream, give origin to infective emboli. With this the necrosed surface layer is exposed, and the bacteria penetrating farther

Fig. 241
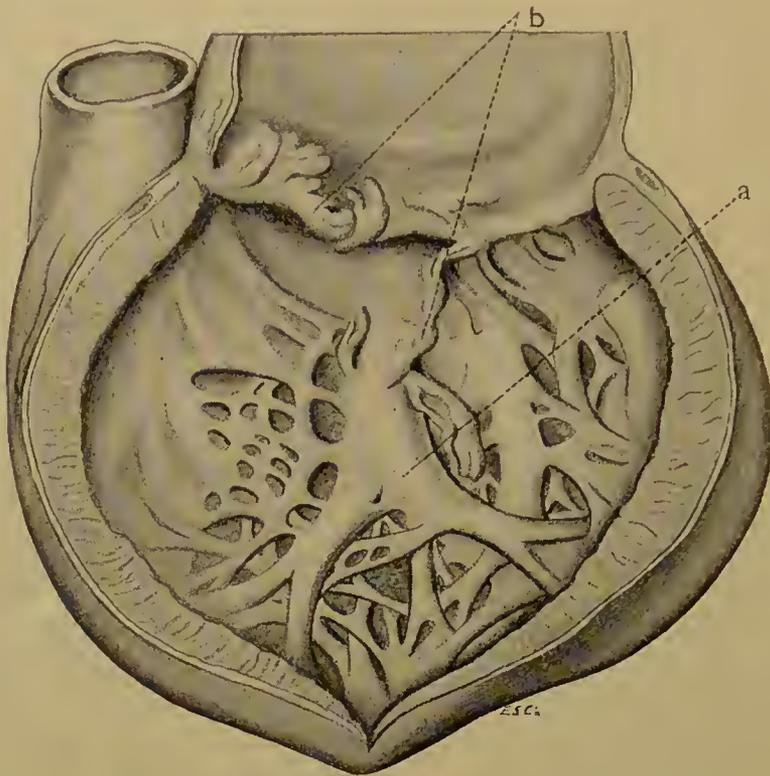
Acute mitral endocarditis with rupture of chordæ tendineæ: *a*, papillary muscle; *b*, ruptured chordæ.

Fig. 242
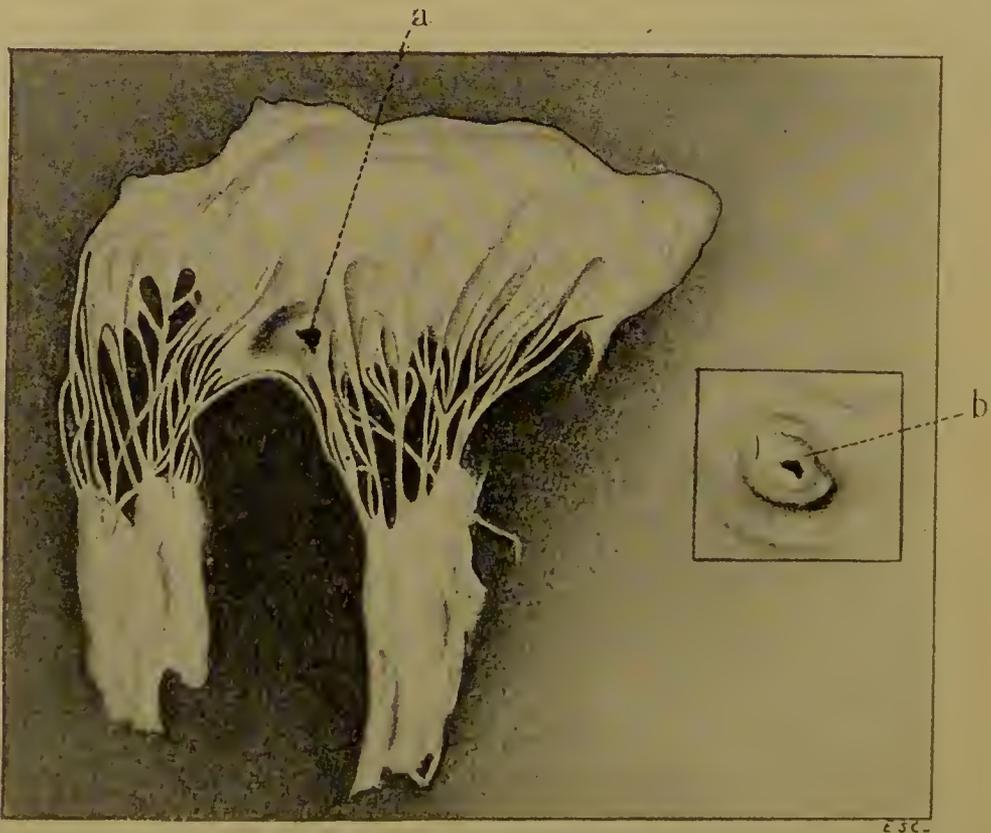
Ulcerative endocarditis with aneurysmal pouching and perforation (*a*) of mitral valve. The same in reverse (*b*).

into the valve substance give rise to an ulcerative endocarditis, accompanying which, with thinning of the valve substance, there may be giving way and development of aneurysmal pouches of the valve (Fig. 242), or without such aneurysm there may be perforation or rupture of the affected cusp. We thus find various grades of acute endocarditis and different observers have differed much among themselves as to the classification of these various grades. It is usual to make a broad distinction between (1) **simple** or **verrucose endocarditis** in which the destruction of the valve tissue is superficial and inconsiderable and also the fibrin formation over the affected areas is very slight in amount; (2) **vegetative endocarditis**, in which the main feature is the extensive formation of thrombotic vegetations, and (3) **ulcerative** or **malignant endocarditis**, in which the dominant feature is the extension of the bacteria into the valve substance, with necrosis and ulceration and their sequels. But while making this distinction it must be remembered that an ulcerative endocarditis may also be vegetative, that there may be areas of ulceration, and surrounding these abundant formation of vegetations. Here once again we have to recognize that we deal with a succession of grades of the inflammatory process, and not with distinct forms of inflammation.

FIG. 243

Aortic endocarditis, ulcerative with aneurysm of sinus of Valsalva (on the left), with perforated aneurysm (*a*) of aortic valve; ulcerations of aortic valves at *b*, *b*. (McGill Pathological Museum.)

Of the different valves the mitral is most frequently involved in the acute process. Next to this is seen a combination of aortic and mitral, and in third place the aortic alone. The tricuspid is least frequently involved.

Chronic Endocarditis. — What we said regarding the pericardium is true with regard to the endocardium, namely, that we can recognize widely different conditions which familiarly, but often faultily, are included under the heading of "Chronic Inflammation," namely, the organizing healing stage of an acute inflammation, the effects of

a recurrent acute inflammation, the effects of granulomatous inflammation, and what is not inflammation at all, the persistent remains or outcome of previous inflammation. The result of an acute inflammation is in the first place a liability for the affected cusp to become vascularized; secondly, if the process be not fatal, there ensue the various stages of healing, with cell proliferation and cicatrization in the area of previous acute inflammation. Thirdly, the vegetations may undergo complete resolution or absorption, or, on the other hand, the organizing process in the underlying valve tissue may extend into them and they may thus become replaced by new connective-tissue formation and may become represented by contracted fibroid nodules projecting from the surface of the cusp.

FIG. 244

Mitral incompetence seen from below, to show shortening and thickening of chordæ tendineæ and large orifice *a*, papillary muscle with attached chordæ so shortened that the muscle impinges upon the valve; *b*, patent orifice of valve surrounded by greatly thickened fibrosed cusps.

The condition that we most frequently refer to as chronic endocarditis is, however, one of diffuse thickening, with contraction and fusion of the cusps, leading either to **stenosis** of the valve, with great narrowing of the orifice, or to **incompetence**, with incapacity of the cusps to meet and

FIG. 245
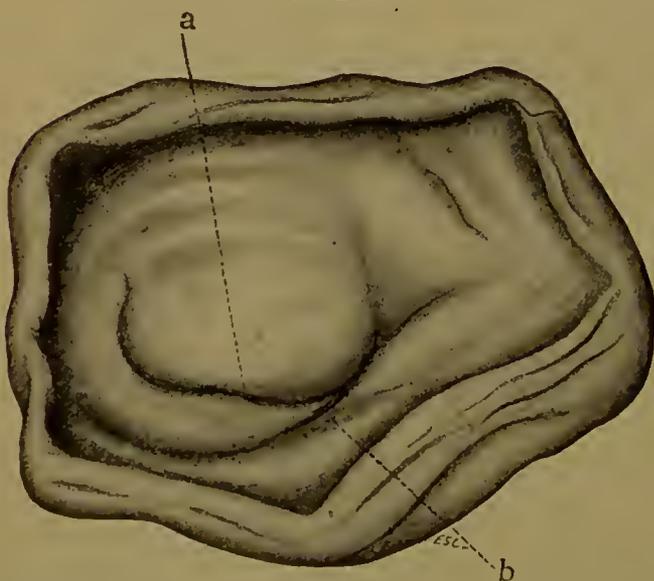
FIG. 246

Mitral stenosis; button-hole seen from auricular aspect: *a*, the slit-like opening hidden by fibrous fold (*b*).

Aortic stenosis seen from above, with fusion of cusps, leaving but a small central orifice.

close the orifice, or often a combination of the two conditions. As regards the mitral valve, which is most commonly affected, it must be

kept in mind that this valve is not composed of two distinct cusps but of a veil of irregular depth hanging down into the ventricular chamber. If we study a series of hearts, we find not a little variation in the conformation of this veil, and, as a result, when this becomes diffusely thickened by new fibrous-tissue formation, in some cases the result is a funnel-shaped narrowing, in others with contraction of the fibrous tissue there develops a slit-like, or button-hole orifice. As regards the semilunar valves we find that the fibrosis affects more particularly the distal portion of each cusp; with contraction, the cusps become much shortened, so that the corpora Arantii, in the act of closure, cannot possibly meet, incompetence and regurgitation being set up. Or, on the other hand, the separate cusps undergo fusion. Where all three become fused marked stenosis is the result (see Fig. 246). It has already been noted that there may be congenital fusion of the cusps, but it must be recognized that such fusion can

Fig. 247
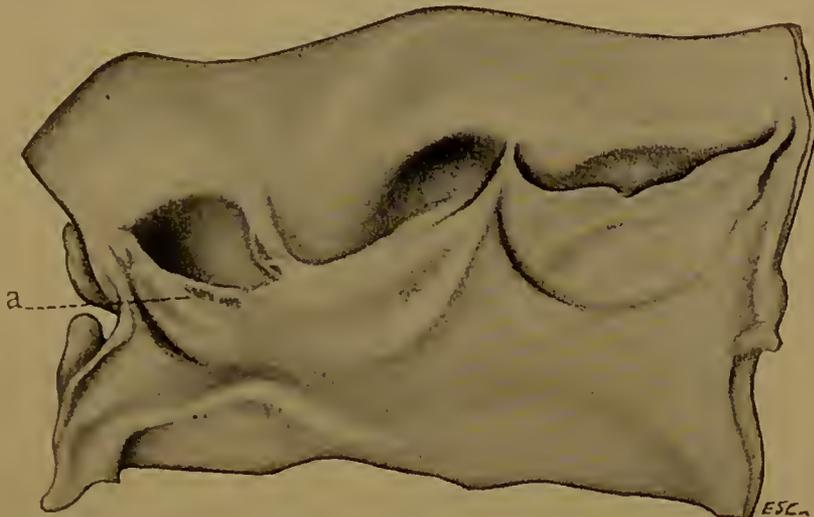
Fusion of aortic cusps. The two cusps at *a* have become united in consequence of progressive slow inflammation originating at the angle of junction.

also occur as the result of inflammation. If the inflammatory agent attack two neighboring valves in the angle of origin, where there is little movement of the cusps, adhesion and subsequent organization may take place, and thus immobility of the cusps, with progressive inflammation involving the angle of apposition, may continue until the neighboring cusps become bound together along the greater part of the area of apposition.

While it is true that **fibrosis** of the valves is a resultant of acute inflammation, we are of opinion that in a very large proportion of cases the thickening of the valves is more of the nature of strain effect than the outcome of previous microbic irritation of the valves. Even in cases of mitral stenosis occurring most frequently in young individuals and then following upon, it may be, recurrent attacks of acute endocarditis, presumably set up by the organism or organisms of acute rheumatism, there is in general wanting any intimate relationship

between the site of the lesions of the acute disease and this chronic thickening, involving the whole area of the valve. The even and regular manner in which the new connective tissue is laid down leads us to the belief that through the localized lesion of the acute disease the valve has been rendered relatively weak and less competent and as a consequence is subjected now to a greater strain, that greater strain leading to a diffuse proliferation of the connective-tissue elements, and consequent thickening and contraction, consequent greater obstruction and increased muscular action with heightened blood pressure, with, in short, the establishment of a vicious circle. In the case of the aortic valve this view gains still greater support, and that because fibrosis of the aortic cusps is more frequent in later life, associated with arteriosclerosis. As we shall proceed to point out, the fibrotic changes of the aortic intima, in the majority of cases, bear no relationship to any infective process, for it must be recalled that the aortic cusps are merely infoldings of the cardio-aortic intima. As actual or relative strain is the cause of the one, we must presume that it is equally the cause of the other. **Rupture** of the semilunar cusps occasionally follows such strain with its accompanying rise of arterial blood pressure.

As in arteriosclerosis, so in these cases of valvular fibrosis, we are apt to encounter a series of degenerative changes—**fatty degeneration** and **necrosis** with **atheroma** and **calcification.**

THE ARTERIES

The arteries may be divided into the two broad groups of those of the elastic type and those of the muscular. The aorta and its main branches belong to the first. In these large vessels receiving the first impulse of the blood wave, and thus liable to sudden expansion, something is evidently needed beyond muscle fibres, both to prevent undue distension and to bring the vessels passively back to the normal when the distending force is removed. We find in the media of these vessels multiple sheaths of elastic tissue alternating with layers of muscle fibres. In the media proper these muscle fibres have a circular arrangement. Immediately within the media, in what is known as the musculo-elastic layer of Jores, there is to be found a small zone of fibres having a longitudinal direction. Smaller arteries are of the muscular type, in which the elastica is often reduced to a single prominent layer, forming the boundary between intima and media; there is often to be noted an external elastic layer between the media and adventitia. It is these smaller arteries, with their relatively abundant muscle layer and capacity to undergo relatively great dilatation or contraction that are the great factor in determining the blood pressure. As to the extent to which the contraction and dilatation of the arteries is under the control of the central nervous system, the evidence before

us indicates that the same conditions obtain as in connection with the heart, namely, we have central influences acting through the vaso-constrictors and vasodilators; there exists also a rich system of nerve cells with processes, forming a plexus in the arterial wall, and, thirdly, the muscle of the media is found to be capable of direct stimulation. The larger arteries may exhibit strong contraction many hours after death and many hours after the vasoconstrictor nerves are no longer irritable. Leonard Hill, more particularly, has called attention to the fact that, under heightened internal pressure, arteries tend, not to expand, but to contract, and this so immediately as to indicate a local and not a reflex reaction. With regard to the nourishment of the arteries the vasa vasorum penetrate only into the outer half of the media, and the internal elastic lamina is seen to oppose a considerable hindrance to much nutritive interchange between intima and media. We must conclude that the intima is nourished from the blood stream, at least the outer two-thirds of the media by the vasa vasorum, while the inner third of the media may possibly receive nourishment from both sources.

Abnormalities.—We have already referred to abnormalities of the larger trunks (p. 470). We may here note in addition that a general **hypoplasia** has been described, with small size of the aorta and main trunks. Some would regard this as truly congenital, and as a condition predisposing to chlorosis, general malnutrition, tuberculosis, etc. Others regard it as secondary to impoverished state of the blood, with weak heart action.

Inflammation.—The arteries may be involved in the inflammatory affections of tissues, their walls often being eroded. That severe hemorrhage does not happen more frequently than it does is due to the fact that the inflammation causes a **thrombosis**. Inflammatory states primary in the arterial wall, especially those due to **syphilis**, will be discussed in connection with arteriosclerosis, by which means that important process, belonging largely to the regressive changes, will be discussed without being divided. Bürger, of New York, has of late called attention to the frequency of an obliterative arteritis (**thrombo-angiitis obliterans**) among Polish and Russian Jews, leading to presenile gangrene of the limbs. Beginning as a migratory localised inflammation with thrombosis of certain veins, eventually both arteries and veins of a limb become extensively thrombosed. The smallest arteries are free, and there is accompanying periarteritis. The cause is unknown.

Regressive Changes.—The observations of Aschoff, Klotz, and Foster show that the thickness of the larger arteries undergoes progressive increase until about the age of thirty-five, then remains stationary until about fifty years of age, after which, in the majority of individuals, a reduction is to be noted. It is the media that in the main shows these changes, and here, after fifty, both the muscle fibres are apt to show beginning atrophic disturbances, leading to shrinkage and disappearance of some elements, and also the elastic sheaths show

greater irregularity in contour and with the disappearance of inter-vening muscle fibres, are apt to run together, forming coarser strands. But beyond this simple **atrophy**, in elderly people we frequently encounter indications of both fatty and calcareous degeneration of the muscle, often associated with a failure on the part of individual elastic bands to take the elastic tissue stain, which may be mistaken for rupture of the fibres. All these appearances indicate that with advancing age the wall of arteries of the elastic type becomes weaker. In the arterioles and smaller arteries **hyaline** degeneration is not infrequent. Both in the media and in the adventitia there is to be noted a deposit or infiltration of a homogeneous hyaline material. Somewhat similar to this, involving not the ordinary connective tissues but the elastic tissues, is the **elastoid** degeneration of the uterine, ovarian, splenic, and other arteries already described (p. 276). **Amyloid** infiltration has a predilection for the muscular coats of smaller arteries as well as the outer surface of the capillaries.

FIG. 248

Fatty streaks of aorta. (McGill Pathological Museum.)

FIG. 249

Nodose arteriosclerosis. Showing fibroid overgrowths of intima around the orifices of the intercostal arteries. (McGill Pathological Museum.)

Arteriosclerosis.—This condition, or as recent German authorities term it "atherosclerosis" or "atherosis," is the most common cause of death, direct or indirect, in those who attain to middle life or, we may say, after thirty years of age. "A man is as old as his arteries," and it is incapacity on the part of the diseased arteries to respond to the needs of one or other organ that leads to malnutrition and atrophy of those organs, even where graver and more immediate disturbances are not produced by distension of the diseased artery (aneurysm), or by rupture of the same (hemorrhage and apoplexy). It is thus all important to have some general ideas regarding the nature of arterio-sclerosis and the conditions leading thereto.

A form of degeneration, frequently observable in those dying from

acute disease is the presence of "fatty streaks" of the aortic intima, white, linear streaks, disposed longitudinally, particularly in the dorsal half of the aorta. Examination here shows fatty changes which may extend up to the intima, but very frequently involve the cells of the musculo-elastic layer. Apparently this represents only a transitory change, and would be recovered from had the individual himself recovered, and that because we are unable to find any chronic developments taking the place of these streaks; Klotz notes occasional intimal thickening over the fatty areas; nevertheless the disposition of these streaks is obviously different from that of the nodes in ordinary arteriosclerosis.

Arteriosclerosis is not in itself a degeneration, even though it may give place to degeneration; it is to be regarded as an adaptive process following upon degenerative changes occurring in the arterial wall.

Forms of Arteriosclerosis.—It may manifest itself in more than one form: (1) the simplest and commonest type is what is known as **nodose arteriosclerosis.** The earliest stage of this, seen in the aorta, presents itself in the form of whitish, flattened, nodular thickenings. It is peculiarly apt to be situated around the orifices of the aortic branches and notably around those of the intercostal arteries (see Fig. 248).

Section of one of these flattened nodes shows that we deal with a pronounced thickening of the intima, in the form of successive layers of new connective tissue. Where the condition is more extensive, similar nodes are irregularly scattered along the course of the aorta and thickenings of like nature, though relatively of larger size, covering, that is, a larger proportion of the arterial circumference, are to be encountered in the various main branches, there, by their very size, leading to some narrowing of the lumen. In the earlier stages, as above indicated, we deal with a simple overgrowth or hyperplasia of the intimal connective tissue. The most abundant nuclei, and the best staining, are present in the layers immediately underneath the endothelium. This indicates that these are the layers of most recent development. As a matter of fact, associated with this development of superficial layers, the deeper layers show evidences of malnutrition, so that very frequently we find either the deeper cells swollen and poorly staining, or that they exhibit fatty degeneration, with granular breaking down and necrosis, and often with some imbibition of fluid, so that the part is distinctly softened and somewhat œdematous, or again this deeper intimal tissue breaks down into a porridgy mass of necrotic material, and if the superficial layer be broken and the soft material be examined under the microscope, it is found to afford abundant characteristic crystals of cholesterin, together with fat droplets and lipoid globules, which are doubly refractive. Or, lastly, such atheromatous areas become the site of calcareous infiltration and deposit, and this to such an extent that there may be formed in the thickened intima a solid calcified plate. The presence of such a rigid

plate in an organ liable to some dilatation results at times in the rupture of the overlying layer of intimal tissue, and the formation, thus, of what is known as an **atheromatous ulcer**. It is interesting to note that there may be somewhat frequent erosions and ulcerations of this

Fig. 250
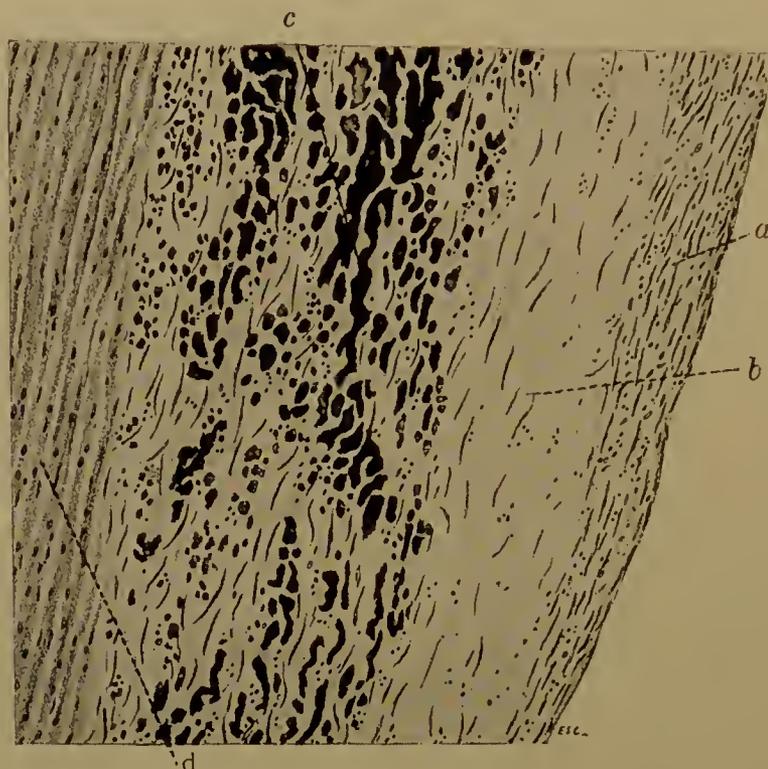
Section through a fibroid plaque of aortic intima from case of nodose arteriosclerosis: *a*, outer proliferating layer of intima; *b*, deeper hyaline layer; *c*, still deeper layers showing deposit of calcareous salts (stained black) and extending into *d*, the inner layers of the media.

Fig. 251
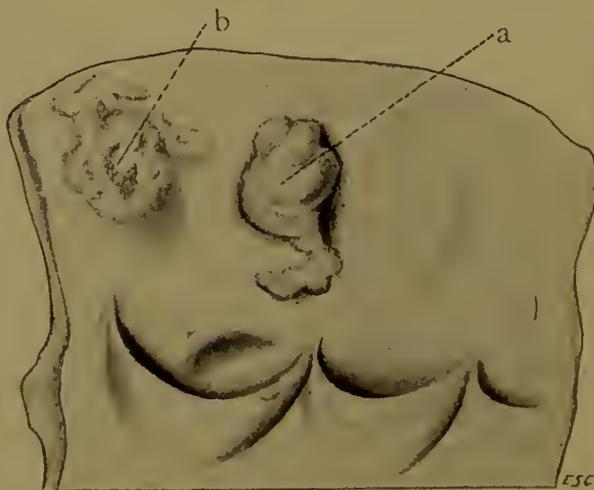
Parietal thrombus (*a*) and atheromatous ulcer (*b*) of ascending aorta.　(McGill Path. Mus.)

nature, with little or no thrombosis formation; occasionally, however, a well-marked parietal thrombus forms upon one of these atheromatous ulcers (see Fig. 251).

The above is the commonest type. The studies of the last few years have led to the recognition of another form, namely, (2) the **syphilitic**.

PLATE XIII
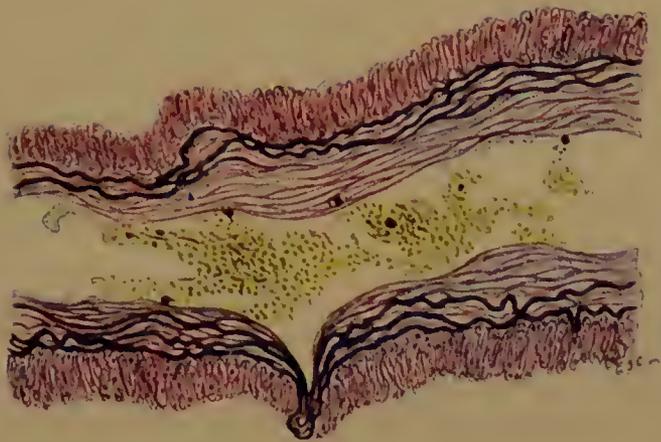
Arteriosclerosis.

Section of a branch of the renal artery cut longitudinally, and stained by elastic tissue stain; showing some hypertrophy of the circular muscle coat, and irregular hypertrophy of the intima with marked increase in the elastic tissue fibrils (stained black).

Whereas the former is found along the whole length of the aorta, and is often most marked in the abdominal section, this second form involves most commonly the ascending aorta and transverse aorta. Here we encounter patches that are of a somewhat translucent appearance, that bear no special relationship to emergent vessels, that often have their long axis transverse, and very often have a puckered appearance. Sclerotic changes of this nature are secondary to syphilitic mesaortitis. It is now abundantly recognized that syphilis finds what might be described as a "point of election" in the vasa vasorum of more particularly the first part of the aorta. There occurs a small-celled infiltration around the branches of these small arteries in the adventitia and media, and this is followed by what might almost be described as a "melting away" of the media in the affected areas (see Fig. 252). One of two results may follow, either (and this when the process apparently is not very acute or very extensive) the weakening of the media is followed by an overgrowth of the connective-tissue elements of both intima and adventitia, or (where the process is more extensive and more acute) in place of such compensatory overgrowth the arterial wall gives way, with resultant aneurysm formation.

Fig. 252
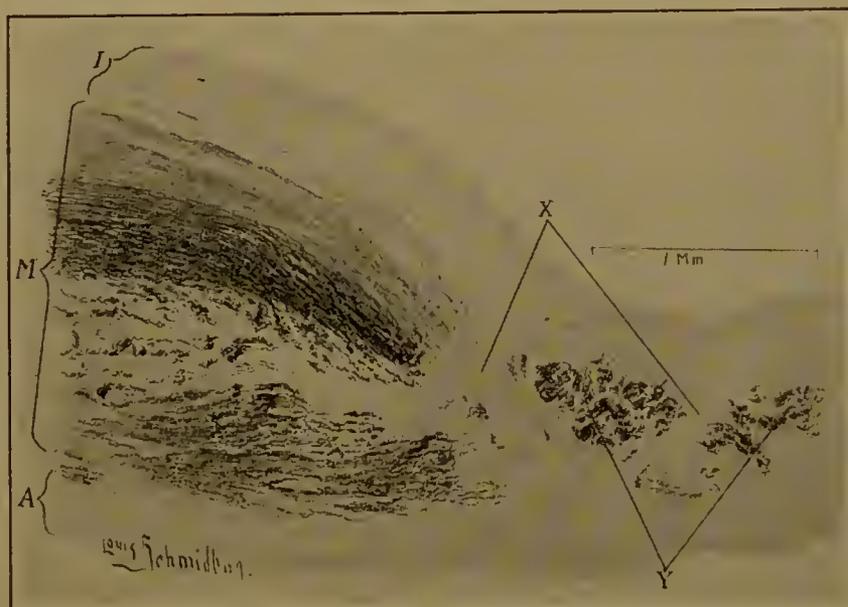
Section from aorta of syphilitic mesaortitis to show extreme degeneration of media and absorption of elastic tissue: *I*, thickened intima; *M*, media, the darkest parts being the elastic tissue. At *X*, this has disappeared; at *Y*, round-celled infiltration.

(3) **Mönckeberg's Sclerosis.**—Here we deal with a process in which the most marked feature, seen in arteries of large size such as the common iliacs, is an extensive degeneration of the media with atrophy of its muscular elements and frequent calcareous deposits in the atrophied muscle cells and, it may be, in the elastic tissue layers. A similar process occurring in the aorta leads to a diffuse dilatation, with elongation and appearance of accessory curves. In the larger branches above noted the degeneration occurs in transverse patches, so that at autopsy

there are to be seen a succession of ring-like or transverse depressions which are very characteristic (see Fig. 253). The important point regarding this form is that a similar calcareous infiltration of the media is apt to involve the smaller arteries; if a series of the well-known "pipe-stem radials" be examined, it is found that their hardness or sclerosis is not due to intimal fibrosis but to this condition of medial calcification preceded often by hypertrophy of the muscular coat. In the larger arteries it is more common to find a combination of nodose sclerosis and this medial degeneration. It must not be forgotten that pipe-stem radials have sometimes after death been found collapsed and soft: in such a case it is presumable that the stiffness of the artery wall was due to spasm.

FIG. 253
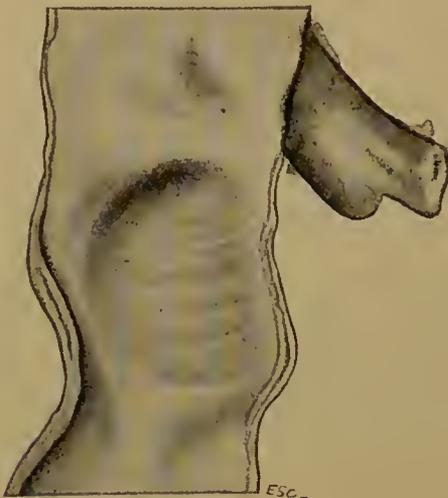
Mönckeberg's arteriosclerosis affecting the external iliac arteries.

FIG. 254

Section of arteriole of myocardium showing the intimal overgrowth of endarteritis obliterans. This is an enlargement of the arteriole seen in Fig. 234.

FIG. 255
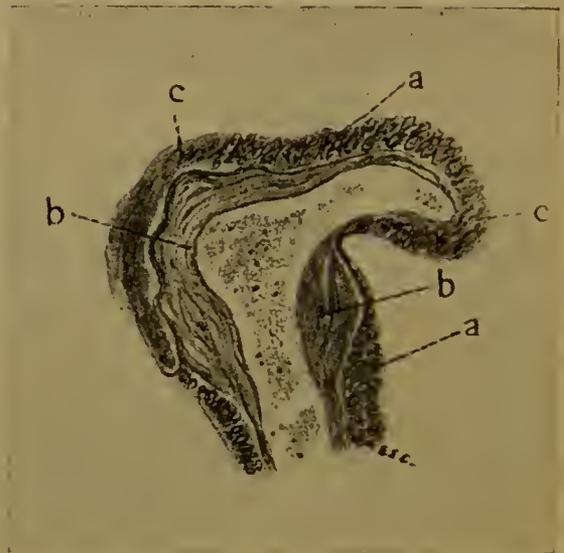
Longitudinal section through a branch of the renal artery, showing the relationship between weakening and atrophy of the media and adaptive overgrowth of the intima *a*, normal or, more accurately, hypertrophied media; *b*, *b*, areas of the thickened sclerosed intima over regions of medial thinning and degeneration; at *c*, the media is disorganized.

(4) **Endarteritis Obliterans.**—All the above changes, including the syphilitic, are found to involve also the arterioles and arteries of smaller size. The syphilitic changes manifest themselves particularly in association with the cerebral arterioles. Here in the earlier stages there is a well-marked, perivascular, small-celled infiltration, accompanied by an

overgrowth of the intima, which may be so extreme as to lead to obliteration of the lumen.

The nodose and Mönckeberg sclerosis present a succession of stages. In the smaller arteries either there is a diffuse hypertrophy of the muscular coat, frequently to be made out in the branches of the renal artery, or apparently following upon this hypertrophy, there is here and there exhaustion and degeneration of the muscle; there is some fibrosis and, in addition, where the muscle has given way, an adaptive overgrowth or sclerosis of the intima, or with diffuse dilatation of these smaller arteries there is diffuse, rather than nodular, intimal thickening; the adventitia of the smaller arteries frequently partakes in these changes, becoming generally thickened (**chronic periarteritis**).

Fig. 256
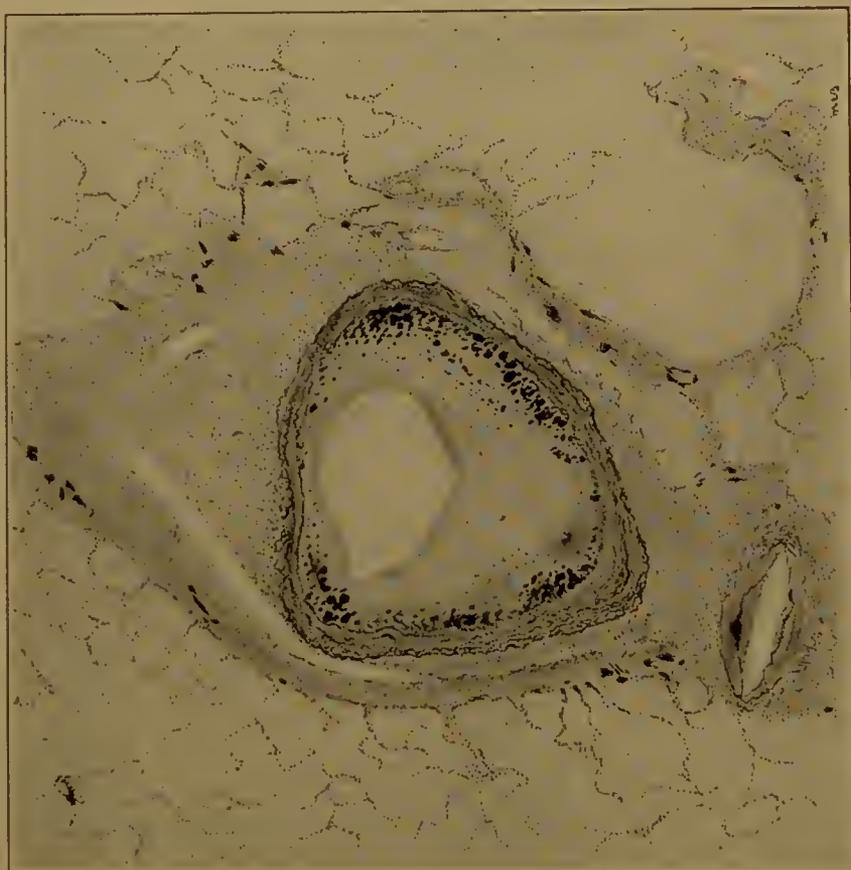
Sclerosis of pulmonary artery. The black dots in the thickened intima represent fat. The lumen of the artery is greatly interfered with—arteritis obliterans. (Prof. Oskar Klotz.)

A very remarkable form of **sclerosis** is seen in the uterine arteries and in the branches of the ovarian arteries of multiparæ, clearly in relationship to menstruation. We have already described this, showing how large masses of elastoid material become formed, together with the regeneration of a new artery within the old one (p. 276). Here again we deal with no infective process, but with a functional

stimulus, leading to active new growth of intimal, medial, and adventitial elements. The process is clearly adaptive.

The observations of Klotz and others show that experimentally, after the intravenous inoculation of certain bacteria or their toxins, there may be developed localized areas of intimal proliferation. More than one observer has called attention to the supervention of arteriosclerotic changes in young adults following upon typhoid fever. Were the organisms of the exanthems and of the commoner infectious diseases the cause of arteriosclerosis, we would expect to find this condition common at or following the period during which these infections are most rife, namely, in childhood and youth. On the contrary, arteriosclerosis is commonest in and after middle age, at a period, that is, when the individual shows a striking relative immunity to infectious diseases.

Etiology.—We thus support the view that arteriosclerosis as such is not in general of infective origin and, indeed, is not an inflammatory process. We hold that it is the expression of a disordered relationship between the internal pressure to which the artery is subjected and the strength of the arterial wall, that strength depending, in the main, upon the condition of the media. The same results ensue when there is increased internal pressure, the wall being of normal strength, and when there is only normal internal pressure, with weakening of the media. Whether this weakening be due to inflammatory infiltration, as in syphilis, or to degeneration, as in old age, is a secondary matter. The tendency will be in any of these conditions for the wall to give way at the point of least strength; if it give way suddenly a complete break or an aneurysm is formed, and, what is more, the intima is overstretched and overstrained and shows little tendency to take on excessive growth. If the strain, on the other hand, be not excessive, it is followed by active proliferation of the intimal connective tissue and this proliferation continues with the laying down of layer upon layer until the new development is so thick and firm that it is no longer subjected to strain. With this the sclerosing process becomes arrested.

In favor of this conception two series of experiments may be quoted: (1) that of Klotz, in which holding up a healthy buck rabbit for a few minutes daily by the hind legs, over a period of four months, the increased pressure brought to bear upon the thoracic and cervical region led to marked hypertrophy of the heart, diffuse dilatation of the thoracic aorta and nodose arteriosclerosis of the carotids, and (2) Carrell's experiment, repeatedly confirmed, of ligaturing a length of a vein in the course of the carotid artery of the rabbit or cat, of replacing, that is, a portion of the artery by a like length of a vein. Performed properly the operation leads to no thrombosis or arrest of blood current, and if the animal be killed some months later, the vein is found somewhat dilated, but showing a most marked thickening, with laying down of fibrous tissue in all the coats, though most markedly in the adventitia. This fibrosis can only be regarded as functional or reactive, as a response to the increased strain thrown upon the vein.

Recently, it has been demonstrated by Cholatow and others, that feeding rabbits with cholesterin and so bringing about an excess of cholesterin in the organism, brings about an arteriosclerotic process in the vessels. The exact significance of these observations has not yet been determined.

Thus, to conclude, we recognize (1) a true inflammatory endarteritis, due to bacteria and their toxins, mainly involving the arterioles, occasionally, and to a slight extent, affecting the aorta; (2) an inflammatory periarteritis and mesaortitis, of which syphilis affords a most striking example; (3) an intimal sclerosis, non-inflammatory in nature, secondary to actual or relative weakening of the middle coat (and there may be an adventitial sclerosis of the same nature); (4) a medial sclerosis (Mönckeberg's sclerosis) of degenerative nature, the hardening being due to the deposit of calcareous salts in the middle coat; (5) a functional sclerosis, as seen in the arteries of the uterus and ovary in which the regeneration and new formation of the arterial coats within the distended lumen of the older artery is accompanied by a hyaline, or more accurately, elastoid deposit outside the newly formed artery, but derived from the internal elastic lamina of the original artery.

Aneurysm.—An aneurysm is an abnormal and circumscribed dilatation of the lumen of an artery. From old time we distinguish between the true aneurysm, in which there is persistence of one or more of the coats of the artery to form the boundary of the dilatation, and the false aneurysm, in which the wall of the artery in the dilatation has become absorbed and the surrounding tissues form a secondary wall enclosing the blood. Following Osler, we may still further classify the forms as follows:

I. **True Aneurysm.**
  (*a*) **Dilatation** aneurysm: (1) **fusiform,** limited to an area of one of the larger vessels; (2) **cirsoid,** involving an artery of the second order with its branches, the whole series thus becoming greatly distended and tortuous.
  (*b*) **Saccular** aneurysm: this is the commonest form, in which there is a localized and lateral giving way of the aorta or of a smaller artery.
  (*c*) **Dissecting** aneurysm: here with rupture of the inner coat the blood makes a passage, dissecting between the layers of the degenerated middle coat, and either makes its way eventually into the pericardial sac or to the exterior of the aorta (leading thus to sudden death from hemorrhage), or back again into the artery at, it may be, some considerable distance from the original site. In this case the new channel gains an endothelium, and the condition may persist for years, the individual possessing apparently a double aorta, and even double iliacs, etc.
II. **False Aneurysm** as above described; strictly the condition is one of hematoma.

Fig. 257
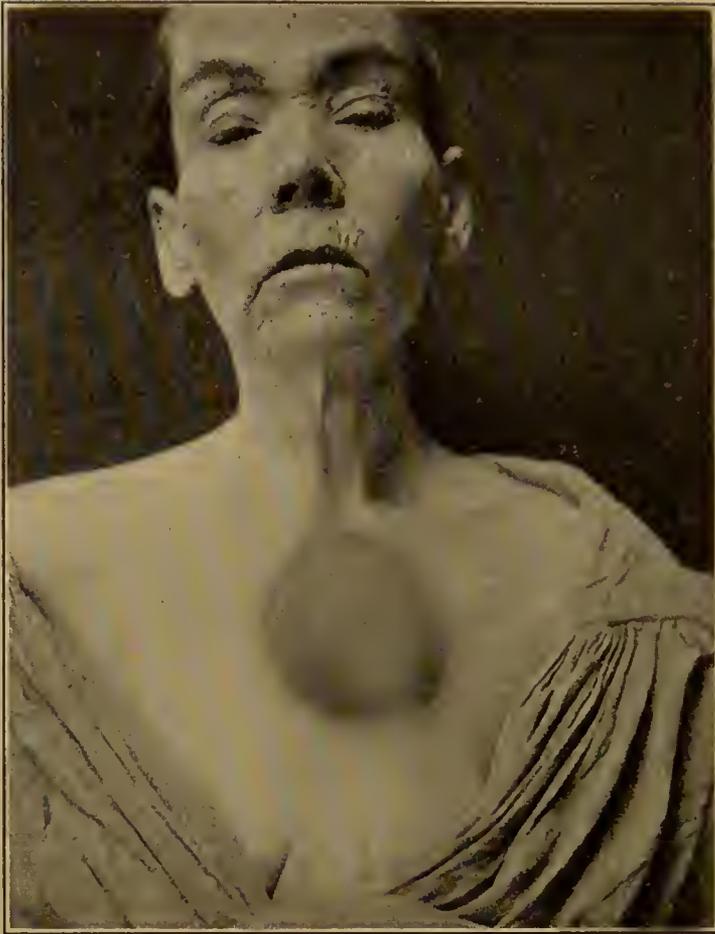
Aneurysm of arch of aorta. The aneurysm eroded and absorbed part of the sternum, and the tumor on the skin was pulsatile and expansile. It burst externally subsequently. (McGill Pathological Museum.)

Fig. 258
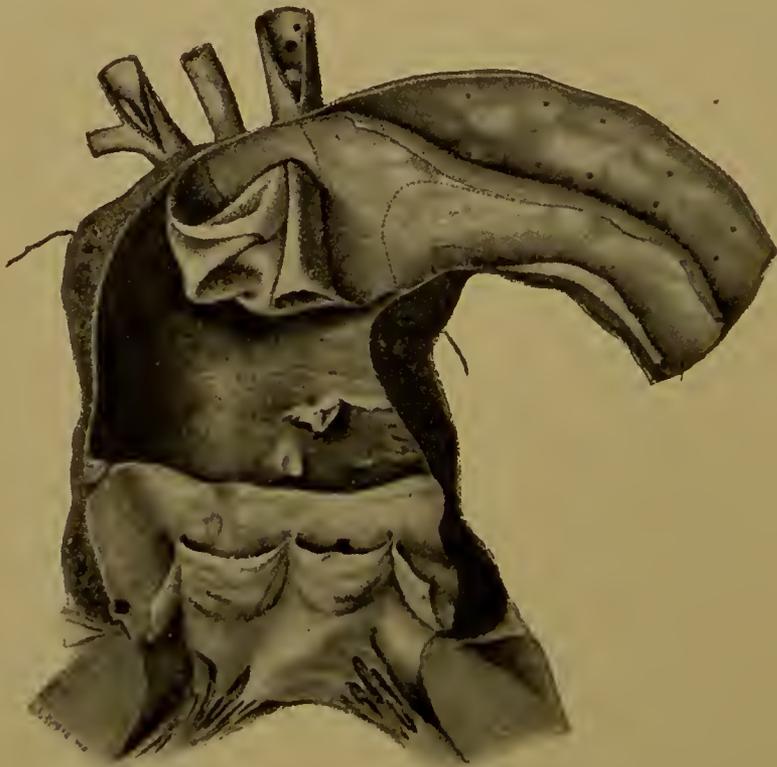
Dissecting aneurysm of the aorta, in which the inner coat of the artery has been stripped off and carried into the opening of the left subclavian artery. (Chiari.)

III. **Arteriovenous Aneurysm** occurs, in which, from traumatic or other causes, there is established a communication between an artery and a vein, either direct (**aneurysmal varix**), a condition in which there is marked dilatation and tortuosity of the vein and its branches receiving the arterial blood, or indirect, a sac originally of the nature of a false aneurysm intervening between the artery and the vein (**varicose aneurysm**).

FIG. 259

Cirsoid aneurysm of occipital artery.   (McGill Pathological Museum.)

IV. **Other Forms.**—There are other forms (rare), such as the **parasitic** aneurysm seen in horses (in which strongyloid worms, present in the blood stream become arrested in one of the smaller abdominal arteries and, growing and setting up irritation in the arterial wall, come thus to fill a sac which is in direct communication with the blood stream); **traction** aneurysms, erosion aneurysms, etc.

As stated in the above table, the commonest form that we have to deal with is the saccular aneurysm; next to this the fusiform aneurysm of the aorta. By far the commonest site of these dilatations is the aorta, and in this the ascending and transverse portions. Aneurysms of the abdominal aorta occur, but are not so frequent; of the main branches of the aorta the popliteal arteries deserve special notice, although the splenic, renal, and other abdominal arteries are occasionally involved. Another site, of no small importance, is the circle of Willis and its branches, while careful examination of the senile brain, particularly in those who have been syphilitic, reveals the not infrequent presence of multiple **miliary** aneurysms upon the cerebral arterioles. Similar aneurysms sometimes follow infective embolism

in cases of acute endocarditis. Klotz recently described a case in which the aneurysms followed rheumatic fever. Both in chronic syphilis and in its more acute condition the infective process leads to a weakening of the walls of the smaller vessels, with consequent giving way under the blood pressure. A rarer form, the so-called **mycotic** aneurysm, is occasionally met with in the aorta; here, apparently, bacteria gaining entrance into the vasa vasorum lead to localized abscess formation in the aortic wall with rupture into the lumen. These, however, are comparatively rare.

FIG. 260
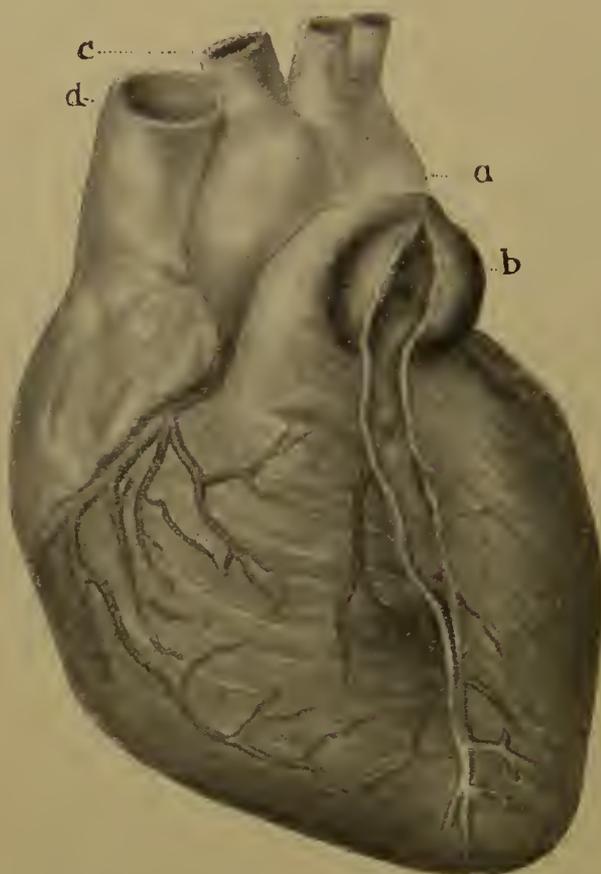
Aneurysm of left coronary artery. (Winkler.) *a*, aorta; *b*, aneurysm; *c*, innominate artery; *d*, superior vena cava.

The commonest cause of aneurysm formation is **syphilis**, and the explanation of the peculiar frequency of the condition in the first portion of the aorta is not merely, as used to be taught, because here the wall is subjected to the greatest internal pressure (though this, of course, is a factor), but because **syphilitic mesaortitis** specially affects this region. The small-celled infiltration around the branches of the vasa vasorum is followed by an extraordinary destruction of the media, the main support of the artery, and it is this localized destruction of the media that is the main cause of aneurysm formation. Extreme degeneration of the media, from non-inflammatory causes, may have the same result, as may arterial trauma or erosion of the outer coats through progressive inflammation in their neighborhood. Thus, where there is cavitation in the lungs with progressive destruction of tissue,

it is not uncommon to find saccular aneurysms of branches of the pulmonary artery projecting into the cavities; but senile, or presenile degeneration, trauma or erosion do not compare in frequency with syphilis, as causative agents.

Results of Aneurysm.—The aneurysm being due primarily to a weakening in the wall, the greater the dilatation, the weaker becomes that wall; there is thus a tendency toward progressive enlargement. If the growth be not too rapid and the enlargement is surrounded by soft, accommodating tissues, there may be a reactionary development of an adventitial capsule arresting further growth. If, on the contrary, the sac impinges upon rigid structures, by compression of the nutrient vessels of those structures, instead of the formation of such capsule, there is a process of necrosis and absorption; the aneurysmal wall becomes so thinned as to undergo rupture, either with extensive hemorrhage and sudden death or with the formation of a localized hematoma

Fig. 261
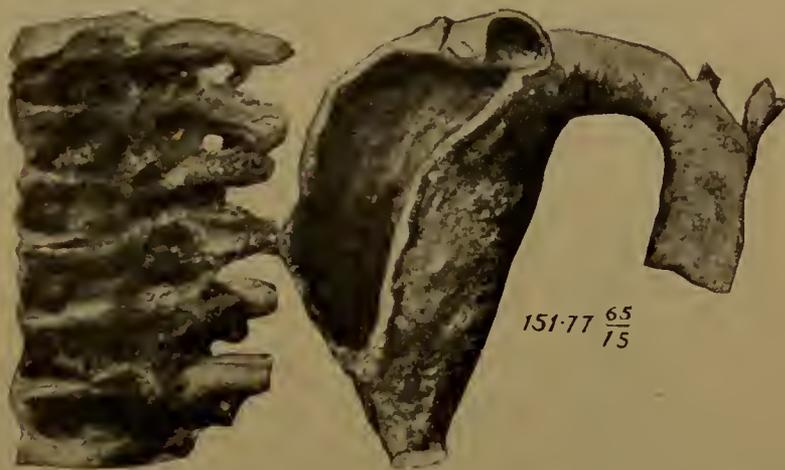
Saccular aneurysm of descending thoracic aorta, showing erosion of the vertebræ produced by its pressure. (McGill Pathological Museum.)

and false aneurysm. Thus, for example, a saccular aneurysm of the ascending arch may completely perforate the sternum, and then form a false aneurysm, pulsating and forming a protrusion in front of the chest, with eventual atrophy of the skin that covers it, and final external rupture. Even in a true aneurysm, sudden increase of pressure, as by exertion, may lead to rupture at some point where the external capsule is thinnest, with resultant sudden death.

On the other hand, if the circulatory conditions are favorable, where, for example, the aneurysm is so situated that the contained blood is relatively stagnant, a process of obliteration may show itself by the laying down of layer after layer of fibrin until the cavity becomes filled up. This complete obliteration of an aneurysmal cavity is, however, rare. Numerous attempts have been made clinically to imitate or induce this natural process, as by temporary occlusion of the artery above an aneurysm, by the administration of drugs lowering

32

the blood pressure and force of the heart beat, and by the introduction of wire, etc., into the aneurysmal cavity, so as to incite coagulation.

Progressive Changes.—In cases of high blood pressure it is not uncommon to find a marked **hypertrophy** of the middle coats of arteries. To this, in recent years, Russell has specially called attention. If the high pressure be long continued this is apt to lead to degeneration of the Mönckeberg type. **Tumors** primary in the arteries are distinctly rare. Some observers have held that uterine **myomas** originate, not from the uterine, but from the arterial musculature. This is still undetermined, and is generally doubted.

CAPILLARIES AND VEINS

Capillaries.—The disturbances of the capillaries have not been studied as closely as they deserve. **Regressive changes** are common and, notably under the agency of bacterial toxins, passive congestion, protein poisons, various mineral and other drugs, the endothelium is apt to manifest a condition of fatty degeneration, which in its turn favors capillary **hemorrhages**. **Hyaline degeneration** or **infiltration** is not uncommon. In our chapter on Inflammation we have called attention to the profound changes that may affect this endothelium as the result of local irritation.

Congenital **dilatation** of the capillaries (capillary telangiectasis) is seen in certain nævi, and similar dilatation may be acquired as a result of active or passive congestion.

The **tumors** that may originate from the capillaries, **hemangiomas** and **hemangio-endotheliomas** have been discussed on p. 397.

Veins.—Regarding the veins the following may be noted: as with the capillaries there may be congenital or acquired **dilatation**. Such dilatation may be diffuse but more often is sacculated (varicosity), with a marked liability to the formation of numerous anastomosing vessels, which become dilated and tortuous. The acquired **phlebectasis** is most often the result of passive congestion, associated with malnutrition, and is apt to show itself (1) in connection with vessels, which, being superficial, lack the support and resistance of surrounding tissues (*e. g.*, hemorrhoids, veins of the lower end of the œsophagus in portal cirrhosis), and (2) in the lower part of the body, where the weight of the column of blood, in addition to the poorer circulation, favors the dilatation of the vessels (*e. g.*, **varicose veins** of leg, pelvic veins, veins of the pampiniform plexus). Such varicosity may be accompanied by reactive thickening of the walls (**phlebosclerosis**), or, more often, by thinning of the same and resultant hemorrhage; the condition of malnutrition favors the onset of inflammation (**phlebitis**), and of **thrombosis**.

Calcification may occur in the venous wall, but it is rare.

Of inflammations, there may be acute suppurative phlebitis; this is usually secondary to a localized suppurative, gangrenous inflam-

mation, as appendicitis, where with infective thrombosis extending
along the veins from the suppurative focus, there may be a progres-
sive ascending thrombosis (**thrombophlebitis**), with associated inflam-
mation of the vein walls. Even in young adults careful examination
shows that a thickening of the walls of the veins of the extremities,
sufficient to render these veins easily palpable, is not uncommon
(*phlebosclerosis*), and this without any sign of inflammatory or toxic
disturbance. We must presume that, as in the case of the arteries,
so here, there may be a strain **fibrosis**.

THE LYMPHATIC VESSELS

Of **abnormalities** the most striking is the condition of congenital
dilatation of the lymphatics and localized areas, apparently due to
some congenital obstruction to the outflow of lymph. Well-marked
examples of these conditions are **macroglossia, macrocheilia, hygroma colli**,
and "**cavernous**" **lymphangiomas** of the superficial lymphatics. Such

FIG. 262

Macroglossia and hygroma colli seen in the same patient. (McGill Pathological Museum.)

lymphangiectasis may also be acquired as the result of obstruction to
the exit of lymph from a region. This may be brought about by the
pressure of tumors upon the efferent lymphatics, or by chronic **inflamma-
tion**, involving and compressing the same, or, thirdly by obstruction
of the lymphatics, as a result of cancerous growth in them. The

most marked and extensive state of acquired lymphangiectasis with its resultants is seen in the condition of **elephantiasis,** very common

FIG. 263

Elephantiasis of legs; lymphangiectasis.   (Collection of Dr. F. J. Shepherd.)

FIG. 264

Filaria sanguinis, with red-blood corpuscles for comparison.   (Simon.)

in the West Indies, and most often the outcome of **filariasis.** The adult filarial worms make their way into the lymphatics, particularly

of the groin, set up there a chronic inflammation with obstruction of the main lymphatic channels. As a result there may be a huge enlargement of the scrotum or lower extremity, in which, in addition to dilatation of the lymph channels, there is an accompanying diffuse fibrosis of the connective tissue, or, again, of the nerve sheaths, and a cutaneous hypertrophy (**pachydermia**). As a result of obstruction, there may also be rupture of the lymphatics, which, when the pelvis of the kidney is involved leads to **chyluria**, when the mesenteric lymphatics are involved causes **chylous ascites**, and when the superficial cutaneous lymphatics undergo rupture brings about the condition of **lymphorrhagia**.

We have already discussed the **tumors** of the lymphatics, namely, the false tumors (**lymphangiomas**), p. 397, and the true tumors (**lymphangioendotheliomas**), together with the rarer **true lymphangiomas**. In this connection we may recall that both carcinomas, and, to a less extent, **sarcomas**, are apt to extend along the lymphatics, and, doing this, may completely obliterate them.

THE BLOOD-FORMING ORGANS

THE LYMPH NODES

These aggregations of lymph tissue are found throughout the body, not only in the large groups anatomically described as cervical, axillary, inguinal, or other nodes, not only as the tonsils, and mixed with various salivary true glands in the region of the mouth, but also as unexpected and variable aggregations on the course of lymph channels and around the veins in any part of the body. The amount of this tissue varies in different ages, and some structures rich in it in youth, as the appendix vermiformis, lose it to a great extent in old age. Its protective function is an important one.

Abnormalities.—A condition still not understood is the so-called **status lymphaticus** of infancy and childhood. In this, accompanying apparently a proper development of the other tissues, there is found a general hyperplasia of the lymph tissues throughout the body and very frequently a pronounced enlargement of the thymus. The causation of this state is most obscure, and some hold it to be congenital.

Circulatory Disturbances.—**Active hyperemia** of nodes occurs in the early stages of infections, and is not so much a step in disease as a preparation for function; the presence of toxins causes a congestion of the lymph node which results in a proliferation of the lymph cells and an increase in their number which is defensive against the near-by infection. **Œdema** of lymph nodes is seen in the case of nodes that are inflamed. **Thrombosis** and **embolism** are of no importance, because the node has a perfect collateral circulation made not only of vessels,

but of lymph sinuses, so that its nutrition can scarcely be interrupted by anything short of a complete cessation of circulation to the part or member concerned. There is one means whereby the circulation through the node can be interrupted, viz., by excessive accumulation of leukocytes and lymphocytes in the sinuses and the proliferation of endothelial cells. This is a factor in producing the central necrosis seen in the bubo and in necrosis of mesenteric and submucous nodes in typhoid fever, but is to be regarded as a useful quality in that it may prevent the generalized spread of a local infection, as is shown below.

Varices are dilatations and tortuosities brought about in the sinuses of lymph nodes, with the final formation of cysts, due to blocking of the efferent channels.

Inflammation.—Lymphadenitis.—If bacteria be introduced into a limb or into a serous cavity they are found in the adjacent lymph nodes within a few minutes. At first they may pass readily through these and be found in the blood; rapidly, however, the node is found to become impervious, to become swollen and congested, to have its sinuses filled with leukocytes, and soon there occurs active proliferation of the lymphocytes of its tissue. Later the endothelial cells lining its sinuses become greatly swollen and enlarged. All these are conditions found in **simple** lymphadenitis, but where the pyogenic microbes have gained entrance in great numbers, the further phase of **suppurative** lymphadenitis is apt to supervene, the nodes becoming still further swollen, soft, and pinkish on section, yielding on scraping a thin, purulent fluid. Central necrosis may occur with the formation of thick pus. These acutely enlarged nodes are known as buboes. Frequently the inflammation affects also the immediately surrounding tissue, which becomes congested and œdematous (**perilymphadenitis** or **cellulitis**).

Chronic lymphadenitis is represented by the enlarged fibrous nodes which are kept in a constant mild state of inflammation by some irritant of moderate virulence, such as is seen in the submaxillary nodes when the teeth are badly preserved; equally well-known examples are seen in **tuberculosis** and **syphilis**, as again in the **anthracotic** nodes at the root of the lung in coal miners, etc. The affected nodes are enlarged, firm, and, according to the nature of the offending material, more or less pigmented. In the earlier stages there is simple cellular hyperplasia, but eventually the capsule and the stroma undergo fibroid thickening which may be so extreme as to cause atrophy of the lymphoid elements proper, the node becoming represented by a dense encapsuled mass of fibrous tissue. In addition to this in tuberculosis, the nodes may be the seat of tubercle formation, with agglomeration and caseation.

Regressive Changes.—Atrophy.—Physiological atrophy of lymph tissue appears to be progressive through life, the lymph nodes being at their maximum in early childhood and diminishing progressively, until in old age the absence of lymph tissue is most marked.

Degenerations and Infiltrations.—Hyaline thickening of the capillary walls and of the stroma is not uncommon in connection with chronic

inflammation, especially in tuberculosis. **Amyloid** affection of the capillary walls is met in general amyloidosis, and more particularly in local amyloidosis such as may be found in the head region. The disease may also affect the fibrous interstitial tissue. **Calcification** is not uncommon in connection with old caseous tuberculosis, while **pigmental deposits**, whether of dust particles or of modified hemoglobin, are very frequent, the former in the bronchial nodes, the latter not infrequently in the deeper mesenteric and retroperitoneal nodes in cases of chronic intestinal disturbances or where hemoperitoneum has occurred. **Tattooing** leads to the presence in the nearest lymph nodes of the pigment or pigments employed. **Necrosis** is met most frequently in the mesenteric nodes at the ileocecal angle in cases of typhoid fever, but may be encountered in various cases of acute infection, bacteriemia, diphtheria, scarlet fever, and bubonic plague.

Progressive Changes.—**Hyperplasia.**—Hyperplasia, as already indicated, is a not uncommon condition wherever a group of lymph nodes is subjected to a mild grade of irritation; it is peculiarly difficult to draw the line between this functional hyperplasia and inflammation, if, indeed, it exists. The particular function of these nodes is to respond to irritants by increased activity which shows itself in lymphocytic proliferation. A compensatory hyperplasia has been noted by several investigators as following excision of the spleen.

Fig. 265

Fig. 266

Section from a lymph node in Hodgkin's disease, showing the different order of cells: a, degenerating leukocyte; b, fibroblast; c, eosinophile; d, lymphocytes, large and small; e, polynuclears.
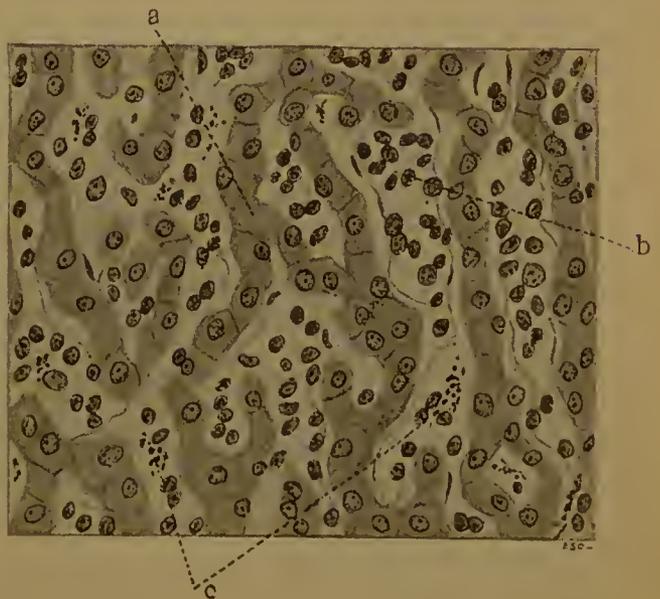
Section of liver from case of leukemia, showing the abundant leukocytes of lymphatic or lymphoblastic type filling the sinusoids or capillaries: a, liver cells somewhat atrophied; b, sinusoid or capillary filled with lymphocytes; c, pigment in endothelial cells.

Hodgkin's Disease.—In this usually there is first noted a progressive enlargement of the cervical nodes which may become extreme, forming huge conglomerate masses; progressively the other lymph

nodes of the body exhibit enlargement, group after group. Macroscopically, the condition differs from tumor formation in that, in early cases, there is a multiplication of different orders of cells, some of them being granular and eosinophilic, while accompanying this proliferation there is a coincident fibrous hyperplasia suggesting strongly that we deal with a chronic inflammatory process. Indeed, there is one type of tuberculous hyperplasia of the lymph nodes which histologically resembles closely the picture seen in Hodgkin's disease proper. The causation of this obscure disease has been dealt with on p. 224. Occasionally, glandular enlargements of the Hodgkin's-disease type exhibit true sarcomatous terminal changes.

Lymphatic Leukemia.—As pointed out elsewhere (p. 357) we are inclined to regard this as primarily a blastomatoid condition, a diffuse and undue excessive growth of lymphoid tissue throughout the body which eventually leads to the passage of an excessive number of lymphocytes into the blood stream.

Tumors.—Such a blastomatoid condition may at times give place to malignancy with infiltrative growth of the lymphosarcomatous tissue through the capsule into the surrounding tissues (**lymphosarcomatosis**), or more rarely in an individual lymph node there may be a primary and local malignant development (**lymphosarcoma** proper). But apart from these true lymphosarcomas, either small round-celled or still more aberrant, large round-celled, or spindle-celled sarcomatous growths may originate from the interstitial tissue of the nodes, or again from the endothelium of the lymph and blood vessels (**lymphangiosarcoma**, **hemangiosarcoma**, and **endothelioma**). In addition to these primary tumors of the lymph nodes, it must be emphasized that lymphoid tissue is one of the seats of election for secondary malignant growths, and notably for carcinomatous metastases.

Hemolymph Nodes.—Attention was first called by Heneage Gibbs, in 1884, to the existence of small nodes, more particularly in the abdominal area resembling in size and distribution the ordinary lymph nodes, but dark in color and differing in that blood replaces lymph in the sinuses. These have since been studied by Swale Vincent, Warthin, and others; they vary considerably in number in different animals of the same species (including man), and Warthin and Meek have explained this by demonstrating that the hemolymph node is capable of conversion into the ordinary lymph node. Their number is increased in conditions calling for increased destruction of red corpuscles, as after splenectomy.

THE SPLEEN

The functions of the spleen are somewhat obscure, but it may be said that it is a "killing ground" for red corpuscles, that it is in foetal life and for a short time subsequently a place of manufacture for the same, and that in case of necessity this function may be reassumed.

It is very vascular, and its arteries open somewhat freely into its sinuses, at areas, the Malpighian corpuscles, where the active proliferation of lymphocytes is favored by this abundant supply of fresh arterial blood. The spleen pulp consists of sinuses lined by endothelium, in which can be seen disintegrating red corpuscles. The splenic veins form part of the portal system, and apparently the amount of relatively arterial blood that can be temporarily contained in the organ is very large. Its capsule is provided with plain muscular tissue, and, as shown by Roy, the organ exhibits a slow periodic contraction and expansion whereby the contents of the sinuses are driven out and renewed.

The spleen resembles the lymph nodes not only in its structure and its function, in short, is physiologically part of the same system, but like the nodes, it has few diseases of its own. Like the nodes, it suffers in general infections, and appears to be to a great extent protective.

FIG. 267
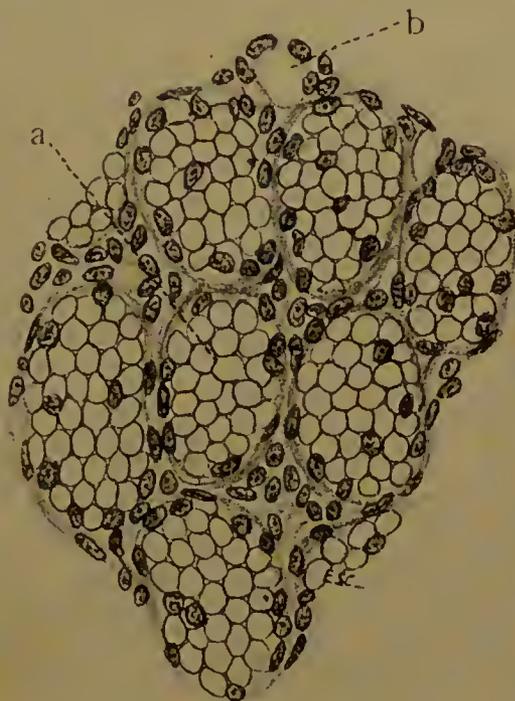
Section from an enlarged congested spleen of chronic obstructive heart disease, showing the sinuses greatly distended: *a*, dilated splenic sinus filled with red corpuscles; *b*, splenic corpuscles.

Abnormalities.—The spleen is rarely absent, but may be very variable in shape and size, and **accessory spleens** are very common. They are usually of small size, and are to be distinguished from hemolymph nodes; they lie oftenest, but not necessarily, near the main organ. The position of the spleen depends largely upon the firmness of attachment of its hilus; in **splanchnoptosis** the mobility of the spleen may be great and it has been seen in almost every possible position in the peritoneal cavity; if increase of its size and weight occurs in combination with laxity of attachment, it tends toward or into the pelvis.

Circulatory Disturbances.—**Anemia** of the spleen occurs as part of a general anemia, and by pressure, and is characterized by a color paler than usual. In atrophic states, to be spoken of later, this color is almost constantly observed. **Active hyperemia** occurs in cases of infection and of intoxication, and is scarcely to be distinguished from the swollen state which will be described in inflammation, of which, indeed, it is the early stage. **Passive congestion** arises in all obstructions to free portal circulation such as happen in cardiac or hepatic disease, and is characterized by enlargement of the organ, with increased darkness of color; microscopically, the sinuses are enlarged, rounded and engorged with blood, there is increased deposit of blood pigment and the connective tissue of the trabeculæ tends to be increased; when the condition of stasis lasts for a long time, the fibrosis is fairly well marked, and the cut surface of the organ is perfectly smooth, glistening, dark red or bluish red, and the organ is dense and firm—**cyanotic induration.**

Embolism, with the formation of infarct, is frequent in the spleen, by reason of the large amount of blood that reaches it, although it is an organ of relatively small size; the embolus is derived usually from the heart valves, and the resultant infarct is often wedge-shaped, with the base outward, of yellowish-white or white color, showing upon the surface of the uncut spleen a raised area (Fig. 268); single or multiple, large fractions of the total splenic bulk may be occupied by infarcts. The infarcted area undergoes coagulation-necrosis, the nuclei becoming hazy and indistinct, while around the affected area is a hyperemic zone of reaction. As in other organs, such an infarct may be completely absorbed and its place taken by a mass of scar tissue. In the case of septic embolus the infarct may break down and abscess result; even as a result of an uninfected superficial infarct, there may be fibrinous exudate thrown out on the surface, of which the ultimate result is an adhesion to surrounding tissues. This is even more certain to occur when the infarct is infected. **Thrombosis** is much rarer than embolism but produces similar results. **Hemorrhage** of the spleen may occur with trauma, but the small hemorrhages seen in the hemorrhagic diseases are not distinguishable, mainly because the spleen is itself filled with blood that is no longer in the vessels; the sinuses normally contain so much blood that a little more is hardly to be noticed.

Inflammation.—**Splenitis.**—Inflammation of the spleen is seen in all severe infections and intoxications, and in some of these, as malaria and typhoid fever, its enlargement furnishes one of the clinical signs of the disease. The spleen is enlarged, and at first firm, the swelling of its elements rendering the capsule tense, so that on section the capsule rips and the contents seem to bulge as if freed from restraint. The cut surface is seen to have lost its distinctness, and the chocolate-colored spleen tissue is seen to be moist and pulpy in its consistence, or at times diffluent. The enlargement may at times be very great, and such a spleen has been known to rupture, either without, or with only slight, violence. Under the microscope, the changes seen are

by no means distinctive. Definite necrosis, especially confined to localized areas, is sometimes seen. **Suppurative** splenitis may occur in the state just described, but oftener is merely the direct result of hematogenous infection in bacteriemia, or of the breaking down of an infected infarct. An abscess may burst through the capsule and initiate a peritonitis, or if small, may be absorbed, leaving a scar, or the pus may remain and become inspissated and ultimately calcified.

FIG. 268
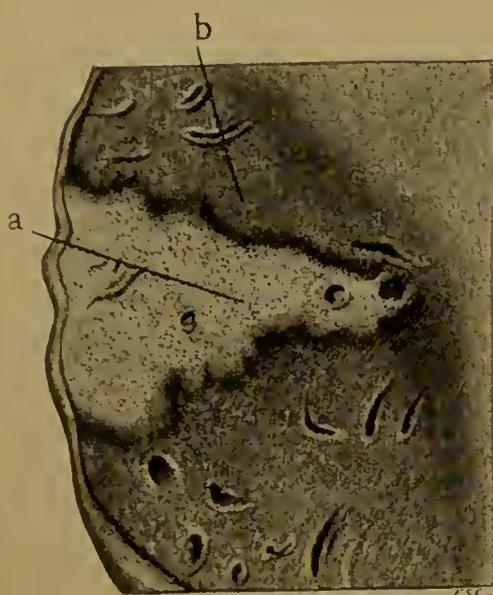
FIG. 269

Section from white infarct of spleen: *a,* infarct; *b,* surrounding splenic tissue with zone of congestion surrounding infarct.

Tuberculosis of spleen with productive tuberculous perisplenitis and caseous tubercles. (McGill Pathological Museum.

Recurrent splenitis is exemplified by the state of the spleen in malaria, where, as a result of often repeated attacks upon the organ by the malarial organisms, many of which undoubtedly ultimately find their way there, a gradual enlargement takes place. In this, as well as in other more chronic affections, there is hyperplasia of the splenic tissues proper as well as of the interstitial tissue, with much increase in size, great firmness of the tissue (**induration**), and increased deposit of pigment; such enlargement constitutes **splenomegaly**. These changes may occur in the spleen in a number of different diseases, malaria, cirrhosis of the liver, syphilis, kala-azar, and especially in Banti's disease. Although there are yet other forms of disease in which the spleen is enlarged, the histological examination of the splenic tissue is not very illuminating, nor does it differentiate one form clearly from another. None of these forms of disease appear to be, properly speaking, diseases of the spleen, although the spleen is always involved.

The **granulomas** are found to affect the spleen. **Tuberculosis** appears in miliary form in generalized miliary tuberculosis, and at times one finds agglomerative and caseous lesions (Fig. 269). While the **syphilitic gumma** is found, the disease is manifested oftenest as a general diffuse splenitis, with enlargement and fibrosis. **Leprosy, glanders,** and **actinomycosis** are found.

Regressive Changes.—**Atrophy** of the spleen is familiar, as it is seen in the old. The organ is small and soft, the capsule opaque and wrinkled,

on section the prevailing color is a pale red, and the trabeculæ appear to be abundant, not from actual increase, but because relative loss of the parenchyma of the organ brings the trabeculæ close to one another. The weight of the spleen is greatly lessened.

Degenerations and Infiltrations.—The spleen is a favorite site for the deposit of **amyloid** in general amyloidosis. The amyloid material appears as translucent small areas of dark brown color, separated by normal splenic tissue; the appearance of these amyloid areas has been likened to that of grains of sago, and the name "**sago spleen**" has been given to the organ thus affected. Where more advanced and diffuse the walls of the sinuses also are involved—"bacony" spleen (see also p. 275).

Pigment infiltration is frequent in the spleen, as will be gathered from what has already been said about its functions in the matter of blood destruction. Apart from already mentioned states, such as malaria, in which it is well marked, is **hemochromatosis** in which there is a marked deposit of pigment in various other parts of the body as well as in the spleen.

Progressive Changes.—Hyperplasia.—We have considered in a brief general way the hyperplastic states and have also mentioned, when discussing leukemia and Hodgkin's disease, certain conditions in which there is an extraordinary development of splenic tissue. In some cases the hyperplasia affects the lymphoid elements, as in lymphatic leukemia; in others, as in Gaucher's type of splenomegaly, the overgrowth involves particularly the endothelial cells lining the splenic sinuses.[1]

Tumors.—Primary new growths are rare in this organ, although various connective-tissue tumors have been reported. Occasionally is found a diffuse **lymphosarcomatous** change, more rarely a nodular **sarcomatous** growth. Secondary sarcoma is not common, though it has been noted in cases of the melanotic variety. It is remarkable how rare is secondary **carcinoma**; primary carcinoma is (naturally) unknown.

THE BONE MARROW

It is difficult to describe the bone marrow as a distinct tissue; there is in it an intimate admixture of cells of various orders. In many respects it is intimately allied to lymphoid tissue, not merely in the existence in its meshes of abundant lymphocytes, but also in general structure. Nevertheless, the existence of abundant leukoblasts giving origin to granular leukocytes (polymorphs and eosinophiles) brings it into a different category, as do also the abundant osteoblasts and megacaryo-

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[1] For the reason that there is diffuse splenic enlargement in many general states it may be serviceable here to tabulate some of the various diseases in which splenic enlargement occurs; we give them roughly in the order of the degree of enlargement that may, as an average, be expected, the most marked enlargement first; myelogenous leukemia, malaria (ague cake), splenomegaly (Banti's), splenomegaly (Gaucher's), lymphosarcomatosis, Hodgkin's disease (late stage), acute infections, chronic congestion, amyloid, syphilis.

cytes. Pathologically it is as a blood-forming organ that it possesses interest.

Circulatory Disturbances.—Anemia in the body generally is, for once, associated not with anemia, but with hyperemia of this particular structure. This is most marked in sudden hemorrhage and in pernicious anemia, the color of the tissue being due not to vascular **hyperemia** but to the abundance of newborn and maturing erythrocytes in the tissue spaces. The marrow in these cases is notably reddened.

Inflammation.—It is difficult to separate inflammatory disturbances in the bone marrow from inflammation in the bone as a whole, such local disturbance being part and parcel of osteomyelitic changes (see Diseases of Bone). The suppurative and granulomatous forms will similarly be discussed in the section upon bone.

Regressive Changes.—With advancing life the amount of red marrow under normal conditions shows progressive diminution, the active marrow cells of the shafts, and elsewhere, becoming more and more replaced by fat cells, until only at the extremities of long bones is any red marrow to be detected, and with yet farther advance in age, the fat being absorbed, its place within the fat cells is taken by a serous fluid so that it becomes translucent (**serous atrophy**). In conditions of **osteitis deformans** along with marked absorption of the trabeculæ the fatty marrow may become replaced by a fibrillar connective tissue with cells lying in a somewhat thick mucoid or hyaline matrix. Associated with this there is a diminution in the number of osteoblasts. The same diminution is seen also in **osteomalacia,** and in both of these conditions active red marrow is characteristically defective.

Aplastic anemia differs from ordinary pernicious anemia in that here also there is an absence of red marrow and of signs of active regeneration of the erythrocytes.

Progressive Changes.—What at first sight seems clearly a **hyperplasia** of the bone marrow, viz., the increased extent of red marrow seen in active blood regeneration as after hemorrhage, is scarcely a true hyperplasia in the sense in which that term is ordinarily used. There is no increase in the marrow as a whole; there is, nevertheless a great production of red corpuscles and coincidently of leukocytes, and also an awakening into activity of cells hitherto inactive, so that where previously there had been fatty marrow we now encounter red marrow. In certain cases of myelogenous leukemia there may be a pyoid marrow due to the excessive production of myeloblasts and leukocytes.

Tumors.—The commonest form of primary tumor of the bone marrow is the so-called **giant-celled sarcoma** (p. 373), a form of myeloma in which the multinucleated cells of osteoclastic type are present in great abundance along with other, uninucleated cells which are polygonal, irregular in size, tending to be bluntly spindle-shaped. As we have pointed out, this differs from the true sarcoma in being relatively benign, so that simple excision in a moderately early stage is rarely

followed by recurrence. **Fibromas, chondromas,** and **myxomas** of the marrow have been described, though they are rare. An interesting form of alveolar growth often wrongly described as primary carcinoma, but apparently more truly of **endotheliomatous** nature, has been reported by several observers.

FIG. 270
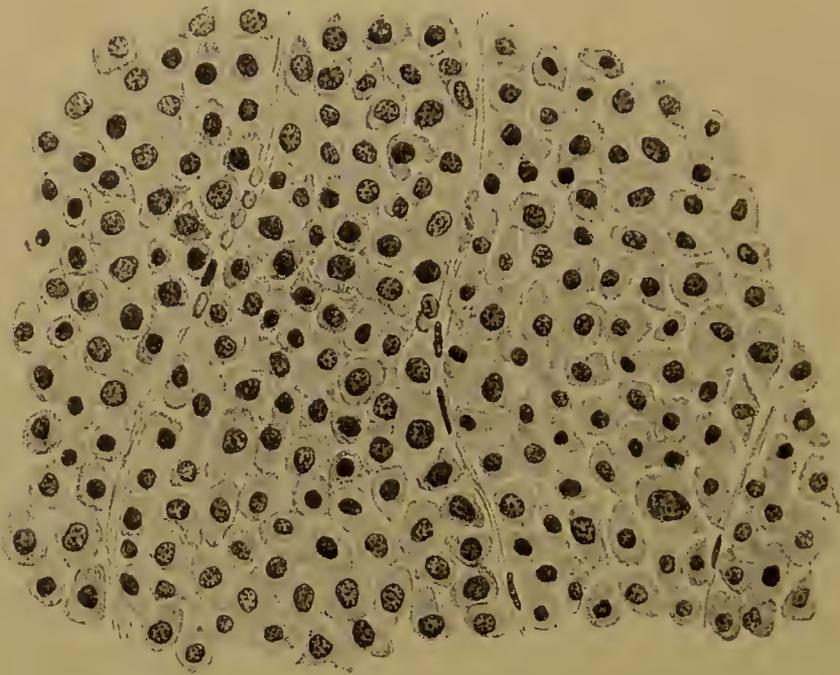
Section of myeloma of vertebra. × 600. (S. Saltykow.)

Myelomatosis (**myeloma multiplex**) is another characteristic form of bone tumor. In this condition, there is the appearance in several bones simultaneously of diffuse, ill-defined growths of sarcomatous appearance; the cells forming these growths show some variation in different cases, perhaps the commonest form being made up of masses of cells not unlike plasma cells. Presumably these are of myeloblastic nature. Uncomplicated cases show no metastases, but occasionally an individual mass may take on malignant infiltrative properties, and when this is the case, secondary growths of sarcomatous type may be found in other organs. Occasionally spindle- and round-celled sarcomas may be encountered, originating in the marrow, the former derived not from marrow cells proper but from the connective-tissue framework.

We must doubt the existence of primary carcinoma of the bone, and, on the other hand, must emphasize the peculiar liability of the bone marrow to become the seat of secondary cancerous growths. Thus careful examination of the head of the humerus shows infiltration by carcinoma derived from the mamma in a large proportion of advanced cases of breast cancer. Certain malignant tumors show a peculiar liability to form metastases in the bone marrow, notably carcinomas of the thyroid and prostate, and hypernephromas.

THE ADRENALS

It is difficult to place the adrenal; its cortex is embryogenetically allied to the cortex of the kidney and the nephric system, but functionally we can find no close relationship to the same. Its medulla is derived from the sympathetic system, but the specific cells have apparently departed wholly from nervous function. The only active property with which so far we can surely say that it is endowed is in connection with its internal secretion, and this has as its most striking feature a remarkable influence upon the arterial tonus; wherefore we have determined to consider it along with the vascular system.

The adrenal is a ductless gland, lying in close juxtaposition to the upper pole of the kidney, abundantly vascular, and consisting of a cortex and a medulla. The former is divided into three zones of which the outermost consists of masses of cells with relatively large nuclei, the **zona glomerulosa**; the middle zone consists of columns of polygonal cells containing abundant fat and lipoids, the capillaries running between the columns of cells, the **zona fasciculata**; the innermost layer is made up of irregular masses of polyhedral cells, often pigmented, the **zona reticularis**. The medulla, of entirely different structure, contains chromaffin cells, with numerous nerve fibrils, being, in fact, closely related to the ganglia of the sympathetic system.

Physiologically we observe, obscurely, it is true, a certain interrelationship between the functional activity of the adrenal, the thyroid, the hypophysis, and the generative system. Further, there is evidently some connection between the adrenal glands and the pigments of the skin (melanins), so that when the adrenal tissue ceases to properly perform its function, there may be an unduly great amount of pigment deposited in the skin.

Abnormalities.—**Hypoplasia** of the adrenals is found at times in those showing failures of development of brain tissue, and in some cases of delayed sexual development. **Horseshoe adrenals** have been seen, and **accessory adrenals** are common; these appear as tiny lenticular bodies on the surface of the otherwise normal adrenal; at times accessory adrenal tissue may be found underneath the kidney capsule, or embedded in the liver substance, or again in the neighborhood of the testis and in the broad ligament.

Circulatory Disturbances.—**Anemia** is unimportant; **hyperemia** of the active sort occurs in infective diseases, and passive hyperemia in general states of blood stasis; with hyperemia, **hemorrhage** is prone to occur, usually punctate, but sometimes of large size (**venous infarct**). Fairly frequently in our autopsies on infants, we have found hemorrhage in one or other adrenal without having any clinical details to correlate with the condition, and in quite a proportion of cases in young children hemorrhage or infarct of one or both adrenals has been the only serious lesion seen to explain sudden death. It seems as if

there were at times symptoms referable to suddenly occurring hemorrhage of the adrenal, viz., a sudden onset of abdominal pain, vomiting, diarrhœa, and collapse.

Inflammation.—Acute inflammation of the adrenal occurs in some cases of pyemia and by extension of inflammation from nearby structures. It seems likely that **cavitation** of the adrenal is often due to roughness in removal of the organ. Softening may, however, occur. Abscesses may appear at times, and sometimes a considerable degree of fibrosis is found.

Infective Granuloma.—**Tuberculosis** is important by reason of its relation to **Addison's disease.** The adrenal may be affected by miliary tubercles, but more often by massive tuberculosis with caseation, affecting one or both organs; here a marked degree of fibrosis is at times to be seen. Such massive tuberculosis is likely to be accompanied by the deposit of pigment in the skin and mucous membranes that characterizes Addison's disease. **Syphilis** has been noted in a few instances, usually as gumma, though there are enormous numbers of spirochetes in the adrenals of the premature congenital syphilitic.

Regressive Changes.—**Atrophy** occurs in the old, but the alterations in size appear to be usually connected with differences in the amount of fats and lipoids. It may be said that no organ in the body varies so little in size from earliest to latest life. **Degeneration** of *cloudy* and of *fatty* nature is seen in states of general toxemia. **Amyloid** disease is found in generalized amyloidosis and **necrosis** is seen in intoxication and locally in **infarcts** from thrombosis.

Progressive Changes.—**Hyperplasia** of one organ may occur in cases of insufficiency of the other, and it has been noted that in destructive disease of the adrenals there may occur a multiplication of chromaffin tissue outside the adrenal, especially in the solar plexus. There is still some debate as to whether in chronic Bright's there be not a distinct hypertrophy, more particularly of the cortex of the adrenals.

Tumors.—Two wholly different orders of tumors originate from the medulla and cortex respectively. Several cases are on record of primary new growths of the medulla which, carefully studied, are seen to be true **neuromas** or **neurocytomas**, resembling in cell arrangement and in the size and appearance of cells the developing sympathetic ganglion (p. 363). In the cortex we obtain tumors of a wholly different order. The simplest and most benign present themselves as nodules from the size of a pea or less upward, originating within the cortex and in structure, formed of columns or cell collections recalling the arrangement of the zona fasciculata. These may be spoken of as adrenal **adenomas.** Several cases are now on record of an intermediate type presenting transition from the above arrangement to a sarcomatous, diffuse, and infiltrating distribution of the tumor cells. In other tumors, again, the capillaries or sinusoids of the new growth become a striking feature and the general arrangement is difficult to distinguish from that of the **hemangio-endothelioma.** Lastly, there may be what seem

to be pure oval- or round-celled **sarcomas**. As we have pointed out elsewhere, we believe that these are all stages or states of development of one common form of tumor, the mesothelioma or, if the term be preferred, the **hypernephroma** proper. Great confusion has hitherto reigned regarding the nomenclature of these tumors. They have been spoken of as carcinoma, as carcinoma sarcomatodes, as endotheliomas, etc.

Secondary **carcinoma** is by no means uncommon, particularly in cases of cancer of the pancreas and stomach. More rarely do we encounter secondary **sarcomatous** growths in the adrenals. Blood **cysts** have been reported after hemorrhage, and **lymphangiectases** occasionally occur in the organ.

THE THYROID GLAND

The thyroids are developments from the floor of the embryonic mouth. At a very early period the connection between the alimentary canal and these offshoots from the same becomes broken and the gland develops through further growths of side processes which in time become dissociated into a collection of ductless vesicles. Even late in life we occasionally encounter in the stroma of the organ small collections of cells tending to develop into new vesicles. Each vesicle presents normally a single lining layer of cubical epithelium and is surrounded by a connective-tissue stroma rich in bloodvessels and lymphatics. Apparently under normal conditions there may be considerable variation in the contents of the vesicles, which show all degrees of consistency up to a dense, inspissated, gluey or colloid material. Upon extraction this colloid material affords iodothyrin, which appears to be the specific product of the activity of this gland.

Abnormalities.—There may be marked variation in the size and relationship of the middle lobe, and in a considerable proportion of cases this shows a remnant of the original median duct in the form of a process of thyroid tissue, the *processus pyramidalis*, passing upward toward the middle of the hyoid bone, sometimes adherent to this by a band-like continuation of connective tissue. In rarer cases there is a direct extension of this to the *foramen cæcum* of the tongue, or the presence of a fistula leading down from the foramen cæcum in the middle line toward the gland. Again, at puberty or even later, cysts may form in the substance of the tongue or between this and the middle lobe; these are lined by glandular epithelium and are evidently remnants of the original thyroglossal duct which have now taken on active secretion. **Accessory lobes** or isolated masses of thyroid tissue are not uncommon. When these occur between the œsophagus and trachea they may cause grave dyspnœa through further enlargement and congestion. A remarkable feature is that occasionally collections of typical thyroid tissue have been found included in one or other part of the bony skeleton, and this without any obvious tumor of the thyroid. They

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appear to be fœtal inclusions. Cases of congenital **hypoplasia** or even of complete **absence** are on record as well as others of congenital **hyperplasia**. These conditions of imperfect function result in delayed growth of the individual and the state of cretinism.

Circulatory Disturbances.—It has been observed that with menstruation and pregnancy, the thyroid shows a sympathetic **congestion** in the female and the great vascularity of the organ makes it susceptible to hyperemic states, so that in passive congestion it may be found markedly enlarged. Cysts of hemorrhagic origin are common in the organ, but this apparently always in association with the formation of local "adenomatous" growths.

Inflammation.—It is somewhat striking that in so vascular and so exposed an organ acute inflammatory changes are rarely noticeable. Abscesses occasionally occur in cases of pyemia, and have even been known in pneumonia and typhoid fever.

Regressive Changes.—The thyroid of elderly individuals not infrequently shows extensive **atrophy** of the parenchymatous elements accompanied with generalized fibrosis, with **hyaline degeneration**, and at times with **calcareous deposits**. In long-continued cases of exophthalmic goitre we obtain evidence that the parenchymatous cells undergo degeneration, possibly from overwork. There are cases on record in which the symptoms of hypersecretion have been followed by those of inadequate secretion or **hypothyroidism**, this being correlated with a form of atrophic flattening of the cells.

Progressive Changes.—The progressive changes of the thyroid are difficult to classify, but the work of recent years appears to be throwing increased light upon the relationship between the different forms. There may be, in the first place, a condition of active **hyperplasia** of the gland associated with increased function and coincident increased formation of the specific internal secretion. This is notable in the enlarged soft gland of early acute cases of **Graves' disease.** In these cases, the alveolar epithelium is prominent, the cells are of good size, and there is evidence of active proliferation of the same in the form of ridges and papillæ projecting into the vesicles. There may even be more than one layer of epithelial cells, and many mitotic figures. Accompanying this, the organ is distinctly vascular and the alveoli are moderately distended by a thin secretion. The picture is identical with that seen in active regeneration of the gland following experimental removal of part of it. Another group of cases exhibits a diffuse enlargement of the vesicles (**diffuse parenchymatous goitre**) but now the epithelium is of a flatter type and the vesicles are distended with dense colloid; the cut surface is gelatinous and there is no markedly increased vascularity. This condition may represent a late stage of exophthalmic goitre with marked amelioration of symptoms or, on the other hand, may develop insidiously, with marked diffuse enlargement of the gland. The very denseness of the colloid and the absence of vascularity indicates that in these cases there is accumulation, in place of increased

discharge, of the internal secretion. Indeed, up to a certain point, such cases may show very little beyond the local effects of the thyroid enlargement and little general disturbance save when, through handling or operation, active congestion is induced and the grave symptoms of hyperthyroidism may supervene. If the condition progress still farther, with pressure atrophy of the epithelium and loss of function, symptoms of myxœdema may show themselves. In yet another series of cases we deal not with generalized but with nodular localized hyperplasia of the thyroid tissue. These are usually spoken of as **adenomas,** a term whose applicability we doubt. They present not so much active overgrowth as a distension of the individual vesicles with colloid. Yet in some cases there is evidence of true adenomatous development. We may thus encounter the **fœtal adenoma,** so-called because in this condition we find areas formed of clusters of cells situated in the stroma, resembling closely the cell clusters seen in the embryonic thyroid. These evidently are undergoing active proliferation, and what vesicles are present among these are of small type and lined by small, rounded or cubical cells. This form according to Wölfler, presents itself as multiple well-defined nodes, originating apparently from mother tissue which has remained latent between the previously developed follicles. The so-called adenomas in their early stages are very vascular and liable to extensive hemorrhages in their substance, which result in the formation of cysts, sometimes of great size. Yet another form has been called by Virchow the **struma vasculosa.** This is not a blastoma proper but merely a great dilatation of the superior and inferior thyroid arteries and their branches, leading sometimes to great enlargement of the organ with pulsation and the development of bruits audible by the stethoscope. This condition is often accompanied by indications of hyperthyroidism.

Tumors Proper.—The proliferative conditions just mentioned may give place to true **adenocarcinoma,** or this may originate without previous observable goitre. Arising thus the condition is markedly malignant, with extensive infiltration of the surrounding tissues, penetration of the trachea and of the veins of the neck, accompanied by rapid increase in the size of the organ and the formation of metastases in the lungs, bones, etc. Loeb and others have described both in man and the lower animals a true **carcinoma sarcomatodes,** namely, a combination of the malignant growth of the parenchyma with coincident sarcomatous metamorphosis of the interstitial tissue. Secondary invasion of the thyroid by malignant growths originating in other tissues is comparatively rare; occasionally there may be direct extension into the gland by tumors of the trachea and œsophagus.

THE PARATHYROIDS

We owe particularly to Sandstrom (1880), Gley (1891), Cristiani (1892), and Cohn (1895) the recognition of the parathyroid glands,

and from the stage in which these little bodies were regarded as undeveloped and latent masses of thyroid tissue, we have passed to perhaps too great a belief in the importance of their function. They are usually four in number, situated either immediately outside or imbedded within the thyroid tissue in the region of the posterior inner edges of the lateral lobes above and below, and, in their histological structure, resemble the embryonic thyroid tissue, with frequent cyst-like spaces. Embryologically it is found that they have a separate origin, being derived as outgrowths of the epithelium of the third and fourth branchial clefts, close to, but distinct from, the points of origin of the lateral thyroid masses. They are 6 to 8 mm. long by 3 mm. in breadth. From their similarity to undeveloped thyroid tissue, it is difficult to state with precision whether certain small masses found in the tissues of the neck between the thyroid and the arch of the aorta are accessory thyroids or accessory parathyroids. These are so common as to make the frequent statements of surgeons that they have removed both thyroids and parathyroids without obvious results of little value.

The observations of MacCallum suggest the existence of a poison in animals whose parathyroids have been removed, which enters into combination with certain cells of the nervous system, so that there develop the symptoms of **tetany**, a condition characterized by spasmodic contractions of the muscles, convulsions, rapid respiration, with dyspnœa and salivation, followed by coma and death. Accompanying this there is increased excretion of calcium salts with diminution of the calcium contents of the blood (MacCallum and Voegtlein), while, as pointed out by Erdheim, the extirpation of the glands in the rat is followed by defective deposition of lime in the large incisor teeth, followed by brittleness and a tendency to breaking. Fracture of the bones of these animals is followed by delayed conversion of the cartilaginous into bony callus, affording a picture that recalls somewhat that seen in rickets. If an animal showing these symptoms be bled, they are checked and can be made to disappear by the injection of emulsions of parathyroid. This condition of tetany in humankind occurs most often in infants and here several observers have noted the existence of hemorrhages in the parathyroids; these, however, are not present constantly and a further condition of gastric tetany is described associated with dilated stomach, etc., in which no lesions have been made out in these glandules. An attempt has lately been made to correlate hemorrhagic and necrotic changes in the parathyroids with marasmus of infants.

Hyperplasias, or so-called **benign adenomas,** have been described, without much evidence of functional disturbance.

CHAPTER VIII

THE RESPIRATORY SYSTEM

GENERAL CONSIDERATIONS

THE chief function of the respiratory system is the intake of oxygen and the discharge of carbon dioxide for the benefit of the economy at large. This is accomplished by the filling of the air sacs with air on the one hand, and the capillaries and lymph spaces with blood and lymph, on the other, and the free interchange of the gases between the two, separated as they are from one another by the alveolar epithelium, the capillary or lymphatic wall, and what connective tissue may chance to intervene. It has been calculated that there are 725,000,000 alveoli in the lungs, exposing a surface of roughly 210 square yards, so that the air cells are lying close to a film of blood that has been estimated to be 10μ in thickness. The amount of gaseous interchange can be thus seen to be enormous, yet this is but a small part of the process of oxygenation of the tissues, for only a small amount of oxygen undergoes reduction in the corpuscles. The cells have an intense avidity for oxygen, and are capable of storing it to some extent, for the tissues have been shown to be capable of metabolism for some time in an oxygen-free atmosphere or when transfused with oxygen-free saline, during which metabolism carbon dioxide is abundantly discharged. The arterial blood is almost but not quite saturated with oxygen, and even in asphyxia some oxygen can still be obtained from the blood. Of the process of diffusion which the oxygen undergoes from the time it leaves the corpuscle until it joins and becomes part of the biophoric molecule we know very little, but we suppose the transference to be fairly direct.

Anatomically, it may be noted that there are abundant elastic fibres in the alveolar walls which assist in the recoil of the lung, in the expulsion of air, and in the circulation of the blood and lymph in the

alveolar walls; that the right bronchus is larger than the left by one-third, and that the bronchial tract has a capacity that is one-thirtieth that of the lungs; that the varying diameters of the larynx and trachea are evidently to impart a rotary motion to the current of inspired air; and that a double blood supply from the right ventricle through the pulmonary artery and from the aorta through the bronchial artery give a very free collateral circulation in all parts of the lung.

The Air Passages.—This term includes the entire tract from the nostrils to the terminal bronchioles, a considerable distance; the effect upon the inspired air is that it enters the air sacs (1) at the body temperature, (2) impregnated if not saturated with moisture, and (3) devoid (normally) of dust and foreign particles, and therefore sterile. The nasal passages have an important effect in bringing this state of affairs about, and the large surfaces of the turbinated bones warm and moisten the air, and their moist surfaces, like those of the whole tract, entangle particles to an enormous extent. If the effect of this mechanism be nullified by mouth breathing, it will be seen at once how serious may be the effects produced upon the lower parts of the tract. Mouth-breathing may result from nasal obstruction of many different sorts— from congenital or acquired narrowness of the passages, from trauma, from the secretions of inflammation or the thickening resulting therefrom, from tumors, especially polyps, and from lymphoid enlargements. Of the last, **adenoid growths** of the nasopharynx are very common and very important; occurring in childhood, they may be associated with peculiarities of development of the nasal chamber, especially a high arch of the palate.

In normal conditions, there is a distinct protective function exerted by the nasal mucosa, which is at once highly sensitive, strongly vascularized, and richly supplied with mucous glands; as a result, the irritant agent may be at once expelled by sneezing, and irritation is followed by marked reaction with abundant mucous secretion, which protects the epithelium, washes off and dilutes the irritant, and supplies a physical impediment to bacteria.

The Pharynx.—Assistance is lent by the pharynx in these processes, and while its surface is not multiplied like that of the nose, the sudden change in direction imparted to the air current assists actively the entanglement of foreign particles; the abundant provision of lymph tissue (including the tonsils) is directed to this end, and it is notable that many of the air-borne diseases, such as the exanthemata, are connected with a preliminary infection of the pharynx.

The Larynx.—The main function of the larynx is phonation. The larynx, essential for the singing voice is not essential for speech; the "note" of the voice is determined by the tension and the rate of vibration of the vocal cords, and by communication of this vibration to the air. The voice is therefore affected by the pathological states of the vocal cords, which may be thus divided: (1) excessive nervous stimuli lead to spasmodic contraction of the laryngeal muscles, with closure

of the aperture; defective or arrested stimuli lead to flaccidity; and (2) intrinsic disturbance of the cords, such as diffuse or local inflammatory thickening, or development of tumors upon them, by which the cords become "muted." Articulation, on the other hand, is dependent on the lips, teeth, palate, and tongue, and it is by disturbances of these that it will be affected.

The site of the vocal cords is the region of the greatest narrowing of the respiratory passage, and at this point, therefore, a relatively inconsiderable stenosis by spasm, inflammatory deposits, or new growths, may assume importance; in addition to this, the larynx, as a whole, is a relatively narrow part of the tract, and even slight affections of the glottis are apt to cause grave obstruction. The relatively loose attachment of the mucosa, except over the vocal cords, renders œdema a common event, in which the upper opening of the glottis, the epiglottic and aryteno-epiglottic folds may be so swollen that unless intubation or tracheotomy be performed, asphyxia may ensue.

The Trachea and Bronchi.—These are lined by moist, ciliated mucosa, which is enabled to take up many particles, and pass them back to be removed by coughing; the trachea is kept expanded by a series of cartilaginous hoops, which allow much mobility of the tube; yet there may be hindrance of respiration by (1) foreign body, (2) deposits or contractions from inflammation, (3) new growths, or (4) pressure from outside, such as would be produced by aneurysm, goitre, mediastinal tumors, and sometimes even by enlarged tuberculous lymph nodes. Valvular obstruction, permitting inspiration but interfering with expiration, may occur with a diphtheritic membrane or a polyp. **Asthma** is supposedly due to a spasm of the bronchi and bronchioles suddenly produced through nervous mechanism; not only is there a spasm so produced, but evidently a rapid congestion which is so great as to amount to angioneurotic œdema with abundant secretion.

Complete obstruction to the air passages ends quickly in asphyxia; with obstruction to inspiration the inspiratory act becomes slow and labored, even to **stridor**, the expiratory act short and unimpeded; the diaphragm contracts more fully, and the accessory muscles all aim at increasing the capacity of the thorax; in expiratory dyspnœa, the abdominal and trunk muscles aim at lessening the thoracic capacity. Where one main bronchus is obstructed, there is rapid respiration until adaptation is secured, after which one lung continues to perform the work ordinarily done by both.

The Muscular and Nervous Mechanism of Normal Respiration.— Inspiration is an active process, and expiration, largely, if not entirely, a passive one, brought about by pressure upward of the abdominal viscera during relaxation of the diaphragm, aided by the elasticity of the expanded lung and of the thoracic wall. The groups of muscles, intrinsic and accessory, and the mechanics of the act will be found detailed in text-books of physiology. The different nerves concerned in the stimulation of these muscles appear to be under the coördinated

control of a centre, although we are unable to say which particular group of cells constitutes this centre. Afferent impulses affect it, for stimulation of many different cerebral areas and peripheral nerves modifies the respiratory act; the pulmonary branches of the vagus are the most important afferent nerves of respiration, and stimuli are apparently generated by the carbon dioxide tension in the blood, increased tension of carbon dioxide stimulating the centre to produce increased respiration, and reduced tension depressing it.

Disturbances of Respiration.—**Sneezing.**—This is a reflex act, caused usually by nasal irritation stimulating a branch of the fifth nerve, and consists of a deep spasmodic inspiration followed by a strong, quick expiration. During the first part of the latter process, the mouth is closed by the approximation of the dorsum of the tongue and the soft palate, so that the first portion of the air that is expelled goes through the nose, tending to drive before it the irritant particles; then the tongue and soft palate are separated, and through this relatively narrow space the air is forcibly driven, producing the characteristic sound.

Coughing.—This is voluntary or reflex, the irritation in the latter case being in the nasopharynx, the larynx, the lungs, or the pleuræ, although it may be in the external auditory meatus; deep inspiration is followed by closure of the glottis, which remains closed during the first part of the strong expiratory effort; the glottis is thus suddenly "blown" open, and the released air may carry with it mucus or other matter from the parts of the tract that lie below.

Dyspnœa.—This term denotes two different states, that of air-hunger, and, more correctly, that of labored inspiration, due to absence of an adequate amount of air, or to the accumulation of carbon dioxide in the blood, with or without deficiency of oxygen. It may or may not be accompanied by cyanosis; the individual is protected by being compelled at once to reduce his muscular activity, diminishing forthwith the call for oxygen and the discharge of carbon dioxide. If the venosity of the blood be acting upon the centre for some time, there develops a lowered sensitiveness of the centre which becomes accustomed to a tension of carbon dioxide that could not be borne if suddenly presented; and there are, on the contrary, states of hypersensitiveness of the centre, such as are seen in hysteria, in which rapid respiration is produced without there being any evidence of a modified gaseous tension.

The conditions in which dyspnœa manifests itself are: (1) conditions of hindrance to the entrance of the normal amount of air, (*a*) in the air passages (foreign body, stenosis, etc.), (*b*) in the lungs (collapse, exudates, growths, cavitation, emphysema, etc.).

2. Diseased states of the muscular mechanism: (*a*) inflammation of the diaphragm or other muscles, (*b*) diseased states of the centres, the afferent or efferent nerves.

3. Where the circulation of the blood through the lungs or the medulla is obstructed.

4. When the inspired air is rarefied, or carbon monoxide is present or carbon dioxide increased above normal, the two latter states reducing the gaseous interchange.

Asphyxia.—In dyspnœa a sufficient gaseous interchange is obtained to support life, but in asphyxia even this minimum is not obtained, and the accumulation of carbon dioxide goes on until the action of the respiratory centre is arrested. Death may follow prolonged cyanosis without struggling, but more often an intense respiratory struggle occurs. In this acute form there is first of all increased amplitude and rate of respiration, followed by relatively great expiratory efforts, with short convulsive inspirations, the expiration being accompanied by violent muscular efforts of the entire body; as this passes off, the respirations become slow and deep; the mouth is open, the head stretched back, and the arms are raised; there is insensibility, the pupils are dilated, and the respirations become slower and slower until death ensues. Coincident changes in the blood pressure are to be noted; there is a marked rise in pressure, the venous blood stimulating the vagus and vasomotor centres, so that the heart is slowed and the arterioles contracted. The heart, poisoned by venous blood, begins to fail and to distend, and the blood pressure begins to fall.

Cheyne-Stokes' Respiration.—This consists, to quote Stokes' own words, in "the occurrence of a series of inspirations, increasing to a maximum, and then declining in force and length until a state of apparent apnœa is reached; in this condition, the patient may remain so long as to make his attendants believe that he is dead, when a low inspiration, followed by one more decided, marks the commencement of a new ascending and then descending series of inspirations." It was originally supposed that this phenomenon marked oncoming death, but such is not necessarily the case. There are two main groups of disease in which it may be manifest—circulatory disease without obvious disease of the brain, and intracranial disease without affection of the heart; some cases of general infection and some narcoses may also show it. It is not possible in the present state of our knowledge to give any satisfactory explanation of the phenomenon; it appears to be what physicists call an interference curve, that is, it is the resultant of waves of one rhythm on which are superposed waves of another rhythm, the second at times augmenting, at other times neutralizing the first.

The Air Sacs.—If one considers broadly the diseased states of the air sacs that interfere with the proper performance of the work of the lungs, these fall into two main groups—those in which the ingress of air into and the egress of air from the air sacs is prevented, and those in which changes in the walls of the air sacs prevent the proper interchange of gases. Diseases of the first order may lead to those of the second.

Air may be prevented from entering the air sacs because they have not been distended (**atelectasis:** ἀτελής, incomplete: ἔκτασις, expansion), or having been distended, they have undergone **collapse.** If of small

extent, this state is of no moment, the other air sacs undergoing compensatory enlargement; even a whole lung may be thus dispensed with, if the change be wrought gradually.

Obstruction to Air.—The air sacs may become filled, and the air they should contain be replaced (1) by serous fluid, as in the cases of acute or chronic congestion, and in pulmonary œdema, (2) by blood, as in rupture of a branch of the pulmonary artery in a cavity or its walls, or in rupture of an aneurysm into the trachea, or in infarct; (3) by water or other fluid from without, as in drowning; or (4) by inflammatory exudate as in pneumonia. The effects of any of these upon respiration depend partly upon the amount of lung tissue involved, and partly upon the causative agent. In hemorrhage the products of hemolysis, or in pneumonia the toxins, may induce a febrile state which of itself will affect respiration, or the effect upon the pleura in the latter disease may be responsible. In pneumococcus infection it has indeed been recently shown that there is a lessened capacity of the blood corpuscles for oxygen, which may be due to the change of oxy- to methemoglobin. With a fluid in the air sacs there is a certain interference with the circulation in the vessels in the walls which are compressed or not according to the greater or less distension of the sac; if this compression of the capillaries affect a specially large amount of lung tissue, the result is a large amount of work thrown on the right heart, with consequent dilatation, and, it may be, hypertrophy.

Changes in the Walls of the Air Sacs Hindering Aëration.—These changes may be atrophic or may consist of interstitial deposits in the walls of the air sacs. Of the former, the most important is **emphysema.**

Emphysema.—This may be **local** or **generalized,** but the mode of production is alike in both. The bronchus or bronchiole has its lumen narrowed, either by spasm or by inflammatory deposit, or by the presence in it of thick secretion; the forcible inspiration followed by the relatively passive act of expiration leaves an amount of air in the sac sufficient to distend it; successive acts of inspiration will distend it still more, and at no time will the sac attain the proper degree of collapse. This constant state of relative distension will keep the capillaries in the wall compressed (Fig. 271), flattened, and elliptical in section; not only do they contain less blood than when they are circular, but the smaller amount of blood is exposed to a larger surface and increased friction. The final result of this is continued malnutrition of the wall, reduced gaseous interchange, diminution of the elastic tissue and of the elasticity of the wall, and atrophy. In this state, the sudden increase of intrapulmonary pressure, behind the closed glottis, at such times as the moment before a cough "explodes," leads to the rupture of weakened walls and several air sacs are thrown into one. Even if the obstruction in the bronchus be now removed, the damage already done is permanent, and there is a want of proper proportion between the (increased) volume of air and the (diminished) area of wall presented by the air sacs. Those air sacs situated at the surface of the lung, and especially at the thin

edges, being relatively little supported by adjoining air sacs, suffer the greatest distension, so that they may be "ballooned" to a very large size.

FIG. 271
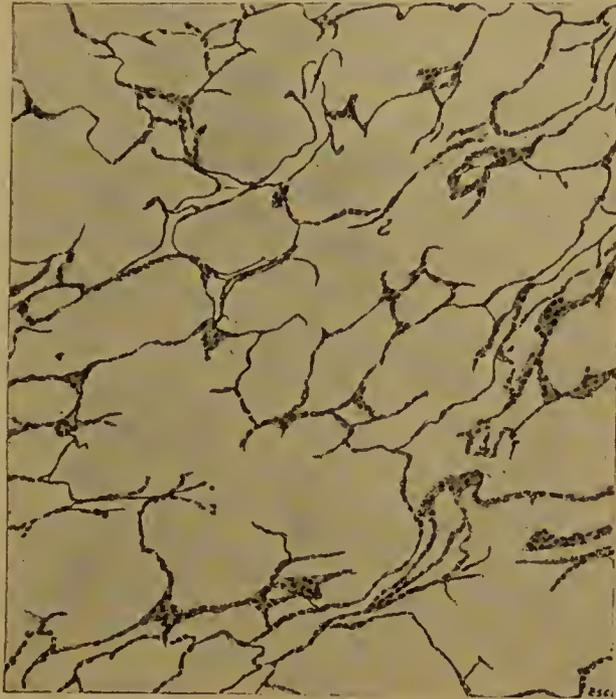
Section from lung showing diffuse emphysema. Note the great atrophy and thinning of alveolar walls and the free ends of ruptured and absorbed interalveolar septa.

We have considered in a general way the causation of emphysema; it will be seen that anything which causes a heightened intrapulmonary pressure may induce this state, hence the liability of players upon wind instruments, of glassblowers, and of persons suffering from such a disease as whooping cough; age, too, has a definite effect, in that the elasticity of the alveolar walls is lessened by the atrophy of the elastic tissue, and proper contraction of the air sac in expiration is not obtained.

With this emphysematous expansion of the lungs, the constant demand for oxygen calls for an overfilling of the already full air sacs, and to obtain this the chest wall comes to assume a barrel-shape, representing the state in which its maximum inspiratory capacity is attained; the expiratory part of the act is lengthened, gaseous interchange is inefficient, the passage of blood through the lungs is obstructed, and embarrassment of the right side of the heart follows.

Bronchiectasis.—This is a condition of the bronchus or bronchiole in which its lumen is dilated in one or many places; either by pressure from within upon an atrophic wall, or by traction from without by contracting fibrous connective tissue, the lumen of a bronchus or a bronchiole may show a fusiform or even an abruptly saccular widening, the enlarged bronchus taking up space that should be occupied by normal air sacs, resulting in diminished aëration of the blood.

Interstitial Deposits. — It is self-evident that new tissue, whether fibrous, granulomatous, or neoplastic takes up room in the lung and by so much displaces normal air space; but this is not all, for it obstructs the pulmonary circulation, so that there is a double interference with the aëration of the blood.

The Pleural Cavities. — These are closed, potential cavities around each lung, and when the two surfaces move freely and smoothly over each other, a uniform expansion of the lung is obtained. If the lungs were fixed to the parietal surface of the chest, as happens in the case of universal pleural adhesions, expansion and contraction would go on but would vary in different regions; thus, with diaphragmatic contraction there would be great expansion of the lower parts of the lungs with little of the apices, and the interchange of air would be slight in that region. There is normally a negative pressure in the pleural cavities.

Pneumothorax. — The entrance of air or gas into one or both of the cavities changes this negative to a positive pressure, and in nearly every case a compression of the lung is produced; in some cases, too, the air drawn in at inspiration is not expelled at expiration, and there may ultimately be a pressure in the pleural cavity greater than that of the atmosphere. We speak of two forms of pneumothorax—**open**, where there is free communication with the external air through the thoracic wall or through the lung, and **closed**, where the opening has been occluded, or where, as in gaseous pneumothorax, no opening to the outside has existed. In open pneumothorax there is necessarily a positive pressure in the pleura, and the lung collapses unless held by pleural adhesions. In closed pneumothorax, according to the amount of air or gas, there may be merely a diminution of the negative or a low positive pressure which is not sufficient to entirely prevent respiration.

Pleural Effusion. — At first consideration one would expect that the effect of an effusion into the pleural cavity would be to diminish the space available for the lung, and that the effect upon the lung would be to prevent its expansion, just as would a positive pressure upon its surface. In effusions of large amount this seems to be the case, and the lung lies against the vertebral column completely collapsed. In small effusions, the fluid by its weight exerts a negative pressure, and the lung, instead of swimming upon the effusion, supports the effusion until its weight exceeds the lifting power of the lung; when this happens, the fluid is able to exert a direct downward force on the diaphragm. In such a case, the partly compressed lung has little chance to exert its elasticity, and the movement of the diaphragm and the costal muscles has to take place against resistance.

SPECIAL PATHOLOGY OF THE RESPIRATORY SYSTEM

THE NOSE

Anomalies.—Malformations of high grade are generally associated with important defects of the face and even of the cerebrum and are important chiefly as curiosities. Practically, the commonest anomaly is a deviation of the bony septum, which occurs with great frequency.

Circulatory Disturbances.—**Hyperemia** of the active sort occurs in inflammatory processes, and in infective fevers such as measles, influenza, and even typhoid fever, and readily leads to hemorrhage (**epistaxis**). Of the passive sort are those hyperemias due to heart and lung diseases, and to the presence of tumors in the nasal cavity. By reason of the delicacy of structure and the elasticity of the mucous membrane of the nose, it is prone to be readily rendered hyperemic in a reflex way, and vasomotor turgescence, even of purely nervous origin is frequent; even so slight a thing as a change of posture in some individuals may cause the disappearance of hyperemia of one side of the nose and its transference to the other. Hemorrhage occurs in ulceration, hemophilia, leukemia, scurvy, suffocation, and trauma.

Inflammation. — **Acute Rhinitis, Coryza, or Catarrh.**—This arises primarily from bacterial infection, and apparently from exposure to cold and wet, as well as irritating chemical vapors. Some persons are susceptible to certain individual volatile substances, such as ipecac, and many to the irritant effect of special sorts of pollen, the smell of certain flowers or animals; the most familiar example of this is **hay fever**, which is evidently a reflex vasomotor effect resulting from anaphylaxis. That coryza is met with in measles, scarlatina, variola, influenza, and typhus fever probably means that a direct infection of the mucosa by the specific agent occurs. The mucosa is swollen, hyperemic, of a deepened color, dry, and irritated, a state soon followed by the copious secretion of a clear, watery, slightly viscid fluid, containing leukocytes and epithelium, and possessed of the power of eroding the skin or another mucous membrane. It must be remembered that such an infection has the power to spread to the throat, the accessory cavities, and sinuses, as well as to the Eustachian tube and the middle ear. In severe primary infections, as well as after the continuance of mild infections, the fluid may become **purulent**, and being so may be mixed with blood and may possess a foul odor. Local abscesses or the erosion of bone or cartilage may follow. **Membranous** inflammation is most often due to the diphtheria bacillus.

Chronic Rhinitis.—*Hypertrophic Rhinitis.*—The long continuance of congestion, either from infection or mechanical irritation, may lead to hypertrophic changes in the mucous membrane. This overgrowth takes place in the submucous tissues, and may, in extreme cases, assume a polypoidal form due merely to the foldings of the mucosa proper. In

some cases such hypertrophy is followed by a secondary contraction leading to a diminution in the size of the turbinate, the so-called "secondary atrophy" seen in old persons. This process, however, is something quite apart from the condition of atrophic rhinitis, as will be seen in the description of that state. The old idea that an atrophic rhinitis is necessarily a late stage of a hypertrophic condition seems to be without foundation.

Atrophic Rhinitis.—This condition has been the object of innumerable discussions and investigations as to cause, and very varied conclusions have been reached. · The condition presents a very definite clinical and also histological picture. The structures in the nose are much shrunken and covered with dry, foul-smelling crusts (**ozena**). The histological picture shows marked thinning of the mucosa, with infiltration and *destruction of the mucous glands*, and also a *metaplasia of the epithelium* from columnar to squamous. There are changes in the bones, which some observers regard as the primary factor in the production of the disease, though this we are not inclined to admit.

Crust formation takes place for two reasons—there is abnormal air space in the nose tending to drying of the secretions, and there is a marked diminution in the amount of these secretions, due to the destruction of the secreting glands.

It seems probable that we have here to deal with a condition having a very varied etiology in different cases. There may be in some cases a congenital peculiarity in the distribution of the squamous epithelium in the nose and in the width of the air spaces, but more often it is probably the result of some former severe inflammatory process which has destroyed the normal lining of the nose, and this has been imperfectly repaired. Such severe destruction may be seen in congenital syphilis, and in the infectious fevers, such as scarlet fever. In some cases a long-continued, latent suppuration in one of the accessory sinuses may be the cause of the diseased state.

The Granulomas.—**Tuberculosis** in the nose is rare; **syphilis**, however, is fairly often seen, beginning with the **"snuffles"** of the baby who is born syphilitic, with a constant purulent catarrh; gumma is apt to arise in the cartilages or bones, and, when broken down, to give origin to the "saddle" deformity so often seen; perforation of the septum and of the hard palate may occur. **Glanders** and **leprosy** may attack the nasal mucous membrane, the lesions varying according to the acuity of the infection.

Progressive Changes.—The most common form of overgrowth is the polyp, and, as has been remarked elsewhere, the polyp is usually not a tumor proper, but a mass of proliferated tissue, which thus becomes **oedematous** or a **myxomatous polyp**. Both are gray, semitranslucent, and sparsely cellular; mucous glands may be enclosed in the mass, and may become cystic; proliferation of the glandular parts may make **adenoma**, of the fibrous parts, **fibroma**, and widening of the vessels **telangiectasis**. One must at times be amazed at the size of oedematous

or myxomatous polyps that can be taken from the nostril. Carcinoma arising primarily is rare, sarcoma more common. New growths, often **endotheliomatous**, arise in the accessory sinuses.

PHARYNX AND TONSILS

Fauces.—As the gate of common entry to two important systems, the digestive and the respiratory, the pharynx is characterized by what would appear to be an extensive defensive mechanism in the shape of abundant submucous lymphoid tissue. This tissue is present over most of its extent, but is massed in the form of very numerous follicles in the two lateral pair of faucial tonsils, and in the median superior or pharyngeal tonsil. The structure of these tonsils is characteristic. The epiderm is relatively thin, and dips down forming a collection of crypts. Both on the surface and immediately beneath the epithelium lining these crypts is an abundant collection of lymph follicles. A smear made with a swab reveals fairly numerous free polymorph leukocytes which have evidently wandered out and ingest surface bacteria, etc. Further, according to Lexer, the thin epithelium covering the tonsils also possesses phagocytic properties. By this means the surface is kept clean and free from the growth of bacteria which have impinged upon it, either from the inhaled air or from the food in the process of being swallowed. It will be further noticed that the submucosa is fairly loose, with a relatively rich vascular supply, and that it contains numerous mucous glands. Notwithstanding these defences the very position and function of the pharynx render it liable to various forms of inflammation.

Abnormalities.—These are uncommon. **Cleft palate** may involve the soft palate; occasionally the uvula is bifid. There may be the openings of persistent gill clefts into the pharynx, these forming either complete fistulæ extending to the surface, or merely closed lateral diverticula. The most striking abnormality is **epignathus** (p. 65). This teratomatous growth, which has its attachment at the base of the skull, projects into the mouth.

Circulatory Disturbances.—The vascular condition of this region and its visibility make it a striking indicator of circulatory disturbances—the active **hyperemia** set up by various irritants, with its scarlet red appearance, through the more brownish color of chronic irritative hyperemia, as in alcoholics and smokers, to the passive hyperemia of cardiac disease, with its bluish-red livid appearance and irregularity of surface brought about by swollen veins. Pharyngeal **œdema** is not uncommon; most often it is associated with spreading inflammatory states, e. g., acute inflammation of the tonsils. It may be angioneurotic in type or may show itself in obstructive heart disease.

Inflammation.—Of this we recognize various grades. It may be noted that local inflammation (**amygdalitis**, of the tonsil, or **uvulitis**) is apt to spread and become generalized, setting up a condition of pharyngitis. We recognize the following forms:

Acute Catarrhal Pharyngitis.—Acute catarrhal pharyngitis or **angina** exhibits in the early stage pronounced redness and swelling of the mucosa, with later abundant discharge of mucus or mucopus and swelling of the isolated lymph follicles, sometimes also of the mucous glands. Over these projections there may be abrasions and formation of small ulcers, with grayish necrotic bases. Acute tonsillitis may be of different types, but in all, the tonsils are swollen and hyperemic, and there is abundant secretion of mucopus. The inflammation mainly affects the crypts which become greatly swollen and filled with foul purulent material. From here the inflammation may extend into the substance of the organ leading to tonsillar abscess, and, as an after-result of the follicular disturbance, the contents of the crypts may become inspissated, cheesy, and intensely foul smelling; still later they may become the seat of calcareous deposits, forming concrements. Where there is abscess formation the process may infiltrate through the deeper tissue extending into the cellular tissue around about, with much inflammatory œdema, setting up the condition known as **quinsy** or, it may be, **peritonsillar abscess.**

Phlegmonous Pharyngitis.—Phlegmonous pharyngitis, whether originating from the tonsils, as above noted, or from trauma, or an acute pharyngeal infection, as in scarlatina, erysipelas, and diphtheria, exhibits a pronounced seropurulent inflammation and infiltration of the pharyngeal submucosa, with extreme swelling of all parts of the pharynx with abundant secretion from or dryness of the surface (which is apt to be deeply congested and to present occasional superficial vesicles). This condition may subside or lead to the formation of localized abscesses, or, again, to a diffuse gangrene of the region.

Retropharyngeal Abscess.—Retropharyngeal abscess of the deeper tissues behind or at the side of the pharynx, may originate either secondary to pharyngitis or tonsillitis, or to caries of the cervical vertebræ, or suppurative otitis media, or, again, may be one of the manifestations of pyemia. Such an abscess is apt to burst into the pharynx, or to extend downward along the œsophagus. Other complications are erosion of the internal carotid or other artery (especially in the case of tonsillar abscess), inflammatory swelling of the cervical lymph nodes, aspiration pneumonia, thrombophlebitis, and general bacteriemia.

Regarding tonsillar and pharyngeal inflammations, there are certain points deserving of note: (1) the high grade of fever that rapidly supervenes even in the simpler catarrhal conditions; (2) the frequency with which acute inflammation of this region ushers in severe general infections, notably scarlet fever and acute rheumatism. In smallpox and measles the pharynx also may be involved and not infrequently secondary syphilitic manifestations of this region lead to an acute pharyngitis.

Membranous Pharyngitis.—It must be kept well in mind that while a characteristic fibrinous or membranous inflammation of the pharynx is due most frequently to the diphtheria bacillus, such membranous

inflammation is by no means a necessary indication of diphtherial inflammation. The so-called "**diphtheritic membrane**" may be due to (1) inhalation of steam and irritant gases; (2) the streptococcus pyogenes; (3) more rarely, pneumococcus, in addition to (4) the most important cause, Bacillus diphtheriæ. In general it may be said that, next to bacteriological examination, the use of diphtheria antitoxin gives the most rapid differentiation between the diphtherial and other forms of inflammation. With this the leathery membrane induced by the diphtheria bacillus may loosen within a few hours. The antitoxin may have some effect on other membranes, but not so rapidly or so characteristically. The true diphtherial infection begins with a localized congestion of the fauces or back of the pharynx; soon there appear grayish-white, opalescent spots, which spread and become fused, and now extending over the pharyngeal wall, coalesce into a dirty yellowish membrane. At the edge of the spreading membrane is a zone of acute congestion, and characteristically the membrane in its early stage is firmly adherent. Removal of the edge or other part will be followed by bleeding. Later, where healing occurs the membrane becomes loosened and may be removed with ease. Such membrane may extend from the pharynx into the posterior nasal passages, the larynx, trachea, bronchi, etc.

As pointed out already, with the superficial growth of the diphtheria bacillus on the surface of the mucous membrane, there is a necrosis and destruction of the epidermal tissue, which is cast off, an intense congestion of the submucosa with abundant exudation of serum and leukocytes, and now a fibrinous coagulation of the exudate, with, at the same time, a necrosis of the superficial layers of the submucosa. As the cells here undergo a coagulation necrosis the resulting membrane is due in part to the surface exudate, in part to these necrosed and infiltrated superficial layers of the submucosa. It is this that renders the membrane so firmly adherent. Later, with healing, abundant leukocytes pass from the vessels into the deeper layer of necrosis, and as these, through their enzymes, cause the liquefaction of the necrosed tissue the overlying membrane becomes loosened. Diphtheria bacilli may be superficial and grow in greatest abundance toward the under aspect of the membrane, although from here they are not to any large extent conveyed to the deeper tissues. Or, if so conveyed, they do not there proliferate actively. Almost constantly there is an accompanying abundant growth of streptococci in the membrane. These may invade the deeper tissues and set up severe complicating disturbances. Rarely the inflammation extends along the Eustachian tube to the middle ear, or through the lacrimal duct to the conjunctiva.

A similar membranous infection occurs in very acute cases of scarlet fever. Here streptococci appear to be the main agents, and the tendency for the process to extend into the deeper tissues with ulcerative disturbances and suppuration of the cervical lymph nodes is much greater.

34

Vincent's Angina.—Vincent's angina, due, it would seem, to the growth of spirochetes with the bacillus fusiformis, is a rare affection, and may in the early stages show membrane formation. This tends to the development of superficial necrosis of the pharynx with the formation of ulcers.

Fig. 272

Spirochetes and fusiform bacilli in Vincent's angina. (Simon.)

Chronic Pharyngitis.—The chronic form may be due to recurrent or long-continued irritation as by alcohol, tobacco, or may be the sequel of a succession of acute attacks. There is a congestion of the pharyngeal wall, with dull, reddish or brownish coloration, a mucoid or mucopurulent secretion tending to dry and adhere in the form of scales, and a hyperplasia of the lymph follicles, giving the wall a granular, warty appearance (**granular pharyngitis**). More rarely with atrophy of the mucosa the membrane becomes thin, smooth, dry, and shiny (**chronic atrophic pharyngitis**). In chronic tonsillitis with advancing age, as again, according to some, as the result of acute tonsillitis, the lymphoid tissue of the tonsils may become diminished in amount, and there may be distinct atrophy of these organs. The opposite condition, hypertrophy, may result from repeated attacks of acute tonsillitis, or from long-continued irritation, as from retention of inspissated material in the tonsillar crypts. In these cases the organs are distinctly enlarged, exhibiting a diffuse hypertrophy, so that they may be of the size of walnuts, and may interfere with swallowing and respiration. General hypertrophy is particularly liable to involve the pharyngeal tonsil in children and thus cause what are generally known as **adenoids**. In fact, the hypertrophic type of chronic disturbance, whether of the faucial or the pharyngeal tonsils especially affects children and brings about marked respiratory disturbance. In a certain proportion of cases what appears to be a simple hypertrophy is found by the inoculation of guinea-pigs to be tuberculous. While this is the case it is interesting to note that there may be no recognizable tubercles or caseation, but a diffuse cellular infiltration, with overgrowth of the stroma of these organs.

As above noted, another form of chronic tonsillitis specially involves the crypts (**chronic follicular tonsillitis**) with progressive distension of these crypts by desquamated cells, etc., until they become filled by large cheesy plugs.

Tuberculosis.—Tuberculosis may involve the tonsils and may, as above noted, be apparently primary, and then of an unobtrusive type, or there may be pharyngeal tonsillar tuberculosis secondary to pulmonary or laryngeal disease. In this secondary tuberculosis of the pharynx the superficial tubercles break down and form shallow ulcers.

Syphilis.—Syphilis in the secondary stage may show itself as an acute catarrhal inflammation, or there may develop mucous plaques tending to give place to shallow ulceration. There are cases of primary chancre, as again of gummas of the submucous tissue.

THE LARYNX AND TRACHEA

Etiological factors of importance in the causation of disease of the larynx and trachea are the character of the respired air, and of the secretions coughed out from below, and the state of nearby organs, such as the pharynx and the thyroid. Finally, it is of interest that the phenomenon of "catching cold" has this physiological basis, that anemia and hyperemia of the larynx can be induced by the application of heat and cold to areas of the skin far remote from the larynx itself.

Abnormalities.—**Absence** of the larynx occurs in conjunction with grave defects that are incompatible with the continuance of life. **Hypoplasia** occurs in the subjects of early castration, giving rise to the modification of voice often observed in such persons. The epiglottis may be fissured, and the sinuses of Morgagni may be so deep as to form definite pouches. The anomalies of most practical importance are **atresia** or narrowing of the tube, **fistulous communication** with the œsophagus and persistence of the branchial clefts.

Circulatory Disturbances.—The laxity of the submucosa is chiefly responsible for the rapid appearance and disappearance of phenomena associated with the blood supply of these parts.

Anemia of the larynx may be an early indication of systemic anemia or even of tuberculosis.

Hyperemia may result from infection, from the effect of dust or irritating gases, and from excessive use of the voice; long continuance of hyperemia may lead to a permanent dilatation of the veins (**phlebectasia laryngea**). Hemorrhage may result from trauma, ulceration, hemophilia, scurvy or phosphorus poisoning, and a hematoma so arising at this site may cause suffocation. **Œdema** of the glottis is the most important circulatory change from a practical standpoint. The acute type is generally of inflammatory origin; the less acute forms arise in patients suffering from cardiac or renal dropsy or from the pressure of cervical or mediastinal tumors or aneurysms. Those parts in which the submucosa is the most lax are most prone to the disease, viz., the aryepiglottic folds, the epiglottis, the false cords, the arytenoid cartilages, and less often the vocal cords.

Inflammation.—**Acute Laryngitis.**—According to the course and the intensity of the inflammation, the appearance of different cases of

inflammation may vary widely, and the most striking feature generally serves to give a characteristic name to the inflammation. Thus we speak of **catarrhal, membranous, phlegmonous,** or **ulcerative** laryngitis, as well as of certain specific forms, such as tuberculous or syphilitic laryngitis, or those occurring in variola, glanders, leprosy, or rhinoscleroma.

Catarrhal Laryngitis.—This represents an early stage of inflammation, seen often by the laryngologist, excited by a variety of irritants, arising in the infective fevers, and is a prominent feature in such diseases as influenza and whooping cough. Just as in the nose, a preliminary redness and swelling are followed by secretion of a fluid at first clear, later cloudy or purulent, not often crusting upon the surface. Superficial erosions are common, and the appearance of traces of blood, from hemorrhage produced by violent coughing, frequent. Influenzal infection is often nasal at first, whereas that of whooping cough is often tracheal. Inflammatory affections of the larynx are assisted and intensified, and even at times inaugurated, by the excessive use of tobacco and alcohol. A definite ill-effect on the larynx cannot but result from the practice of "inhaling" the smoke of even the mildest tobacco, to say nothing of the probably increased absorption of nicotine that occurs through the delicate mucosa of the tract lower than the pharynx.

FIG. 273
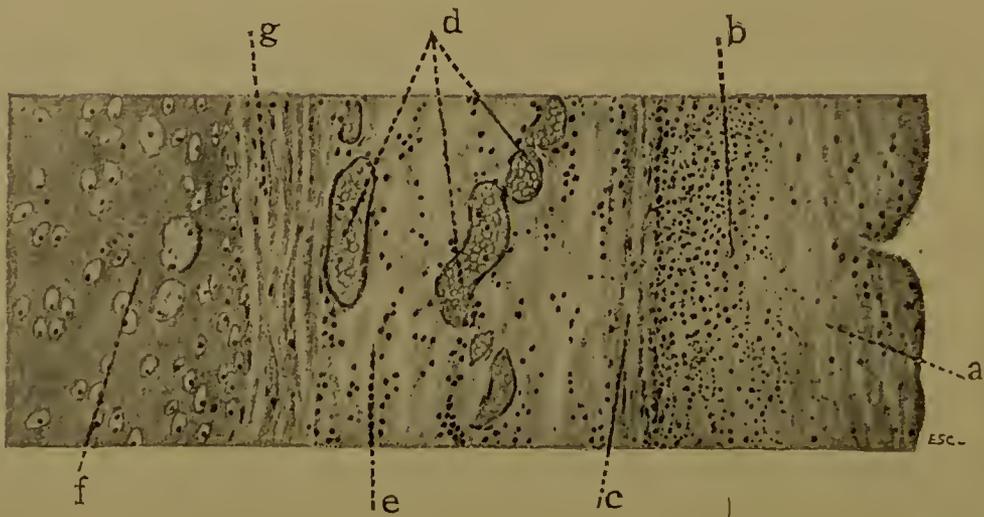
Section from a case of membranous tracheitis; *a*, membrane replacing mucosa; *b*, outer layers of submucosa, necrotic and infiltrated with leukocytes; *c*, muscularis mucosæ; *d*, engorged vessels of submucosa; *e*, deepest layers of submucosa; *f*, cartilage.

Membranous Laryngitis.—The membrane, due to whatever cause, consists of fibrin, moist with serum, entangling in its meshes leukocytes and dead cells of the part, as well as bacteria. The superficial cells may be killed and form part of the membrane; a coagulation necrosis may have gone down to some depth, and layers even lower than the mucosa be comprised; in such a case, the membrane being pulled off, brings with it the upper layers of the underlying tissues, and a bleeding surface results; of this form of inflammation, diphtheria gives a good

example, but it is by no means safe to rely upon this as a sign by which to recognize diphtheria, because a membrane overlying columnar epithelium is more readily removed than a membrane of like density over squamous epithelium, and diphtheria may exist with any sort of membrane or even without one; and, on the other hand, the pyogenic cocci are capable of causing a membrane not distinguishable in appearance from that of diphtheria.

Phlegmonous Laryngitis. — Phlegmonous laryngitis is an occasional sequel of ulceration, or even of diphtheria or erysipelas, and may reach the cartilages, setting up a perichondritis; in this last, sequestration of a part of the cartilage may occur, and a fistula remain.

Chronic Laryngitis. — Chronic laryngitis, of non-specific order, leads to a definite hypertrophy of the mucosa and submucosa,

Fig. 274

Suppurative perichondritis of larynx: *a*, infiltrated and necrotic inner wall of abscess; *b*, cartilage laid bare and surrounded by abscess cavity.

which is sometimes quite localized into warty, gray areas (**pachydermia laryngis verrucosa**); these latter are often found on the vocal cords.

Tuberculous Laryngitis.—It happens frequently that in advanced pulmonary tuberculosis the larynx becomes infected from the bacillus-laden sputum, with the result that ulceration or a diffuse infiltration results. A tubercle, caseating and discharging, will leave an ulcer, or there may be shallow erosions whose relation to the tuberculous infection is not at once evident, or there may be a diffuse, granular overgrowth, definitely tuberculous, which may subsequently caseate in a number of places.

Syphilitic Laryngitis.—Like tuberculosis, this may be evidenced by congestion, a diffuse infiltration or the formation of gummas, the epiglottis and the vocal cords being liable to show the lesions. The tissues sometimes become rough and warty with the overgrowths, and in parts where there is considerable ulceration a good deal of deformity may result.

Glanders, leprosy, actinomycosis, and **rhinoscleroma** are all able to give origin to ulceration of the larynx.

Regressive and Progressive Tissue Change.—Atrophy of mucosa, submucosa, muscle and cartilage, calcification of cartilage and such changes occur in natural or premature senescence. Of progressive changes, the commonest is the **papilloma** or **papillary fibroma**, a warty

excrescence often seen on the vocal cords, consisting of fibrous tissue overlaid by squamous epithelium, which often recurs after it has been removed yet does not often show indications of carcinoma. Like this is the more flattened **nodular fibroma** which is scarcely papillate or polypoid, found on the vocal cords of singers. **Enchondroma, lipoma, myxoma, lymphangioma, adenoma, cysts,** and even **thyroid** tumors are found in the larynx and trachea, and **carcinoma** is the most frequent malignant growth, usually of the squamous variety. **Sarcoma** is rare, and the larynx and trachea are not usual sites for secondary growth.

FIG. 275
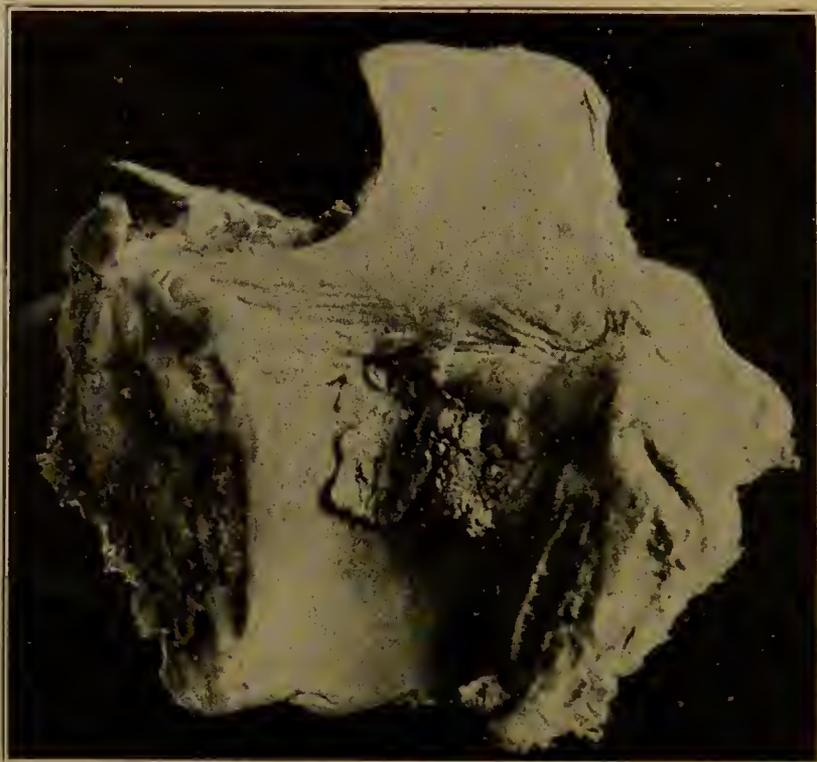
Carcinoma of the larynx. (From the Pathological Museum of McGill University.)

Alterations in Size and Shape.—Obstruction of the lumen may be caused by œdema, inflammatory infiltration, tumors, exostoses, and **atresia,** or narrowing, by contraction of scar tissue, or as the result of pressure from the outside by agencies such as thyroid tumors, peritracheal abscesses, enlarged lymph nodes, or aneurysms, most of which may also cause perforation of its walls.

THE BRONCHI

The pathological changes found in the bronchi are diverse, according to the anatomical nature of the part affected; the larger bronchi, approximating to the structure of the trachea and larynx, are likely to be subject to changes similar to the changes seen in those structures, while the terminal bronchioles are so intimately connected with the

air sacs of the lungs that lesions of the latter are certain to affect the former.

Circulatory Disturbances.—**Passive congestion** of the bronchi is found typically in connection with valvular diseases of the heart; the mucous membrane and the underlying structures are swollen, the surface is deep red in color, and an increase in secretion is seen. Petechial **hemorrhages** occur in severe inflammations, in those suffering from severe systemic infections and in instances of hemorrhagic diathesis.

Inflammation.—Bronchitis, while often universal, is not necessarily so; in the larger tubes it is generally associated with tracheitis, in the terminal bronchioles with lobular pneumonia. It arises by extension from the trachea in all or any of the conditions in which tracheitis is found, including the infective fevers, while it constantly accompanies emphysema, bronchiectasis, and pneumonia, and is almost certain to accompany the development of the passive congestion in heart disease. The bronchi are reddened, covered with a mucoid or a purulent secretion, in which latter case squeezing the lung tissue leads to the expression of tiny drops of mucopus from the openings of the bronchioles.

Acute Bronchitis.—In the simple **catarrhal** form hypersecretion is a frequent, though not a necessary characteristic, for a small amount of sticky mucus may be seen in cases of so-called "dry catarrh." In cases where secretion is abundant it is likely soon to become purulent, and in cases of passive congestion, especially where there is œdema, there may be a very abundant, thin, watery secretion, the so-called "serous catarrh."

Purulent Bronchitis.—In cases that do not quickly recover, this may be a disease of serious import, for the walls become infected with putrefactive organisms, and the purulent secretion may become intensely fetid, and the likelihood of destruction of the bronchial wall and consequent abscess, is increased. This is the so-called **putrid** or **gangrenous bronchitis.**

In **fibrinous bronchitis** there may be desquamation of the epithelium, congestion, œdema, and infiltration of the submucosa, while on the free surface there is an abundant exudate, fibrinous and richly cellular, which in sections of the lung is often seen to fill the bronchus completely. Such a microscopic picture does not necessarily mean that the bronchus is impervious to air. At times tree-like fibrinous masses are expectorated or are found in the bronchial tract after death. It is worthy of note that in bronchial asthma, a clear, glassy, viscid secretion is expectorated in "pearls," which are found on closer examination to be capable of extension into a long spiral around a central thread; as the tube cast is a "cast" of the urinary tubule, so the "Curschmann's spiral" is a cast of the bronchiole. Neither this, nor the "Charcot-Leyden" crystal, is pathognomonic of asthma.

As in the larynx and trachea, membranous bronchitis is usually, but not always, the result of infection by the diphtheria bacillus.

Chronic Bronchitis.—The point of most importance in which this differs from the acute form is that it tends to be productive, the wall being definitely hypertrophic; even the mucosa may be rough and polypoid, due to the irregular contractions of areas of fibrosis. Yet in a very long-continued inflammation, the products may be absorbed, and the mucous glands, muscles, and cartilages atrophy, so that the bronchus may finally be dilated and thin-walled. The specific forms of bronchitis scarcely differ from tracheitis and laryngitis from the same causes—tuberculosis, syphilis, etc.—unless it be in their greater rarity.

FIG. 276

Fibrinous bronchitis. Cast of expectorated fibrinous exudate. (Pathological Museum, McGill University.)

Foreign Bodies, etc.—A foreign body, inhaled, is likely to fall into the right bronchus, because it is larger and more vertically situated than the left; if it completely obstruct the bronchus, collapse of the part of the lung supplied will follow; if the body inhaled be septic, or if the trauma be considerable, a putrid bronchitis and abscess may be quickly set up; at the best, there is likely to be localized inflammation and ultimately a fibroid induration. **Broncholiths,** masses of inspissated secretion in which lime salts have been deposited, are occasionally found, especially in bronchiectasis.

Progressive Tissue Changes.—The hypertrophy which may result from chronic bronchitis seems to form a starting point for many kinds of tumors, such as **chondroma, osteoma, myxoma, lipoma,** and **adenoma,** which have been observed to occur relatively frequently in bronchiectasis. On the whole, however, benign new growths of the bronchus are very rare. Both **carcinoma** and **sarcoma** of the bronchi occur as primary growths, although infrequently. Careful study shows that, following chronic inflammation, the bronchial mucosa is liable to present areas of metaplasia from cylindrical into squamous epithelium, and some

of the cancerous growths show epitheliomatous tendencies. Secondary growths of both orders are often seen.

Alterations in the Lumen.—Perforation.—Perforation of the bronchus may arise from foreign body or from inflammation, while caseation of lymph nodes, carcinoma of the œsophagus, abscess or aneurysm may break in from the outside.

Occlusion.—Foreign bodies, masses of secretion, moist or dry (broncholiths), intrabronchial tumors, or the contraction following a syphilitic ulceration may occlude the bronchus; or from without, the pressure of enlarged lymph nodes, of mediastinal tumors, or aneurysms may bring about a similar effect. If the obstruction be complete, the air in that part of the lung is gradually absorbed by the blood and collapse follows; whereas, if it be only partial, the alveoli are dilated, and emphysema ensues.

Bronchiectasis.—This is a diseased state in which the bronchi are dilated and often distorted, by reason of increased intrabronchial pressure combined with weakness of the walls of the tubes; the resulting enlargement may be single or multiple, local or generalized, and according to its form one recognizes **saccular, cylindrical, fusiform,** and **varicose** dilatations. The wall may be atrophic or hypertrophic, and within the lumen is seen to be encircled by ridges, which represent the less yielding muscular and elastic parts of the wall, while the more yielding connective tissue has given way. The hypertrophic form is found most often in a highly fibroid lung in which an irregular, heightened pressure is found as a result of some parts of the lung being cut off entirely from their supply of air and the pressure in other parts being correspondingly higher than normal; pleural adhesions, too, may be so situated as to pull upon a bronchus in two opposite directions at the same time.

The existence of a bronchiectasis is usually evident to the naked eye; even if the dilatations are not of very great size, it may be possible to trace the tubes almost to the periphery of the lung, and their mucosa is almost certain to show evidences of the accompanying bronchitis, while collapse, compression, cavitation, or induration of the neighboring lung tissue may be visible.

THE LUNGS

Abnormalities.—The anomalies of the lungs are unimportant; variations in the lobulation, especially of the right lung, are often seen.

Circulatory Disturbances.—Œdema.—Where death has been slow, there is almost certainly to be found some œdema of the lungs, which arises from the laxity of the vessels of a failing circulatory system assisted by the toxic or infective manifestations that we have previously referred to as likely to occur in the last hours of life. The lung is heavier and firmer than normal, and on squeezing it, a thin, watery fluid exudes. In this fluid there are no constant cellular elements,

but accidental blood corpuscles, leukocytes, or lining alveolar cells may be seen. This is the so-called **agonal œdema.**

Congestive Œdema is found accompanying passive hyperemia, the posterior (dependent) parts of the lungs being most affected; the fluid, from long continuance of the congestion may be mixed with blood or blood pigment. **Inflammatory œdema** may be found in the early stage of pneumonia, in the vicinity of pneumonic areas, and sometimes in cases of bacteriemia; cellular elements are often present, and the fluid is more albuminous than in the previous forms. The most interesting, and the least understood form is **acute fulminating œdema,** which may come on very suddenly with dyspnœa and the free expectoration of large quantities of thin, watery sputum; it seems to be the result of a sudden rise of pulmonic blood pressure, and is associated with aortitis and other forms of arteriosclerosis. Experimentally, the injection of adrenin sometimes causes it in animals. Microscopically, œdema of the lungs is not shown by any change of the tissue, although if the fluid be strongly albuminous, the coagulated albumin may be seen as a uniform structureless shadow in the alveoli.

Hyperemia.—Hyperemia or passive congestion of the lung arises when there is obstruction to free outflow of blood from the lungs, or when there is deficient heart power; in many cases, respiratory movement is weak, and there is damaged heart muscle, in which case the combination is responsible. The blood is allowed to remain in the lesser circulation longer than it should normally; this stagnation, or slow circulation, is most marked in the dependent parts of the lungs, the posterior halves of both the lobes in the recumbent, the lower halves of the lower lobes in those who sit; this postural type is called **hypostatic congestion.** Obstruction to the outflow from the lungs may be due directly to a valvular lesion, such as a stenosis of the mitral valve, but more often it is due to an unemptied state of the left auricle, from whatever cause. Wherever the heart is incompetent, it is to be remembered that the step that follows incomplete emptying of the left auricle is passive congestion of the lungs. The congested lung is enlarged, firm, less elastic than usual, and of a dark red or purple color; with long continuance, a fibrosis of the lung occurs, and from the dark color and the increased firmness, this has been called **cyanotic induration.** Where much blood is broken down in the course of a long-continued congestion, the pigment stains the tissues and the predominant rusty color leads to the term **"brown induration"** being employed. In such a lung, there are seen in the alveoli, or in the fluid expressed from the squeezed lung, large, flat cells, generally circular, laden with brown pigment granules—the "cells of heart failure" or "cardiac" cells, which are the desquamated cells that in their lifetime lined the alveoli. The microscopic appearance of the congested lung is readily interpreted; the vessels in the interalveolar septa are congested, tortuous and varicose, and seem to jut into the alveoli in a succession of bead-like projections. Blood corpuscles are apt to appear in the alveoli. With this, there is an increase

of the fibrous tissue of the interalveolar septa, which are often richly cellular, the increase being due to the numbers of fibroblasts. Very characteristic are the "cardiac" cells mentioned above, and in long-standing cases the pigment is not confined to these but is seen in the septa themselves.

Hemorrhage.—Blood free in the lung is usually from the pulmonary vessels, but it may be aspirated from the nose or mouth or may come in from an aneurysm external to the lung; one of us (McC.) has described an aortic aneurysm expanding in the upper lobe of the lung. This, however, is a rare occurrence; the common mode of production of pulmonary hemorrhage is by erosion of a vessel in tuberculous or other ulceration or its rupture by trauma. In tuberculous cavitation the blood vessels being very resistant may be left projecting into a cavity as a loop or even crossing from side to side. Such a vessel is unsupported, and its wall being degenerated a rupture may ensue, or an aneurysmal dilatation which later ruptures. Death does not so often result from a single large hemorrhage as from the effect of repeated hemorrhages.

Infarct.—An infarct is the area in which a hemorrhage occurs as a result of the blood supply to it being cut off by a clot lodged in the vessel supplying it. The typical infarct is cone-shaped, sharply defined, the base of the cone usually situated at the pleural surface, the apex innermost at the point where the clot is lodged; it is elevated above the cut surface of the lung, is dark red or purplish, and firm. The pleural surface is at first smooth, but becomes roughened by the fibrinous deposit that results from reactive inflammation. The edges are usually sharp, and with the lapse of time may become gray from fibrin and leukocytes, while the centre may (rarely) soften. Microscopically, the air sacs are distended with blood corpuscles, and the relation of the septa to one another is unchanged; the nuclei of the tissue cells may stain poorly. At the periphery of the infarctous area leukocytes are usually abundant.

With the lapse of time the infarct tends to be absorbed; with the breaking up of the corpuscles and the setting free of pigment the alveolar spaces begin to be reëstablished, and circulation restored. Should infection occur, abscess will follow, but necrosis and cicatrization are not common in the lung.

Arising as infarcts do, in valvular diseases of the heart, it may be that the capillary walls are degenerated, and rupture is brought about by the force of the collateral circulation acting on the capillaries that are full (from the bronchial arteries). It is still debated whether the hemorrhage occurs *per rhexin* or *per diapedesin*.

Embolism.—Although this is dealt with in connection with the vascular system, it may be pointed out that fat embolism occurs in the lungs in the case of fracture of a long bone, where fat is picked up by the blood from the marrow; in fresh tissue the fat globules may be seen and stained in the vessels. Particles of fibrin or even large thrombi may be de-

tached from the systemic veins, and, passing through the heart, may lodge in the lung; if a large vessel be blocked, instant death may be the result.

Diseased States Due to Disturbance of the Respiratory Function.— **Atelectasis.**—This is the state in which the air sacs are partially or completely undistended by air. Complete airlessness is called **apneumatosis.** The true atelectatic state is that in which the lungs have never been distended; in it the bronchi are lying in folds longitudinally, and the alveolar walls are in contact with each other, to be thrown apart and distended with the first breath inspired. A persistence of the fœtal state, with a failure of proper expansion, may be found in debilitated and premature children, especially those with such a developmental defect as hypoplasia of the lung or a diaphragmatic hernia; or with bronchial obstruction by foreign body, by meconium, or by secretion or by compression of the thorax. Not only in infants does atelectasis occur, but in weakly or moribund adults it may arise.

FIG. 277

Section from an infarct of the lung, showing central portion. The alveolar walls stain poorly; the alveoli are distended with blood in which are occasional pigment-holding cells, staining deeply.

When there is a mechanical cause allowing the egress but not the ingress of air, the respiratory act is not of itself sufficient to produce a state of airlessness, but the residue of air that cannot be expelled is slowly absorbed by the blood until the alveolus, being empty, collapses completely, with what may be regarded as a compensatory dilatation and congestion of the vessels of the alveolar walls.

External pressure upon the lung or a part of it induces a **compression atelectasis.** Fluid or air in the pleural cavity, an elevated diaphragm, a mediastinal tumor, enlargement of the heart or pericardium, thickening of the pleura or distortion of the spine may all be effective, not only by reason of direct pressure but also by indirect interference with proper respiration.

When the whole lung is atelectatic it lies high up in the thorax, close to the spinal column, possesses the bulk of a moderate sized adult fist, and is brownish red in color, or if anemic, is gray. From its resemblance to flesh it is sometimes called "carnified." It does not crepitate, and it sinks in water; if squeezed below the surface of the water, a few bubbles may be expressed, chiefly from the bronchioles. If only a part of the lung be atelectatic, the surface of that part is smooth, dark, and depressed below the surface of the rest of the organ.

In the fœtal state, the lining cells of the air sacs are polyhedral or rounded, and project from the walls; with complete expansion of the lung they become flattened, and with a subsequent acquirement of the atelectatic state, they once more assume their former shape.

Emphysema.—The term **interstitial emphysema** describes the state in which the tissues of the body at large or the connective tissues of the lung are infiltrated with air, while emphysema, pure and simple, denotes the overdistension of the air sacs. When this is generalized, there are certain well-marked physical peculiarities in the thorax. The accessory muscles of respiration are well developed, the neck appears short and thick, the chest is enlarged, especially in the anteroposterior direction, so as to be barrel-shaped, while the abdomen is relatively sunken. Upon opening the thorax the lungs are voluminous, relatively of light weight, and do not collapse. The tissue is inelastic, less crepitant than normal, keeps the imprint of the fingers and feels like "a bag of feathers." On the surface, the pigmentation appears slight, the surface pale, and at times the individual air sacs can be seen with the naked eye like little vesicles. In advanced cases, especially at the edges of the lungs, individual sacs may become of great size, giving the lung a bullous appearance (**bullous emphysema**).

Microscopically, as seen in Fig. 271, p. 523, in a case of emphysema there is marked atrophy of the alveolar walls, and many of them are ruptured; several alveoli are thus thrown into one, and the resulting sac takes a shape approximating to the circle. In the thinning-out and rupture of the walls the blood vessels necessarily are flattened, thinned out, and many are thus obliterated; the diminution of space that occurs in the remaining vessels due to pressure throws increased work upon the heart and the right ventricle distends and hypertrophies.

Inflammation.—Pneumonia.—Here consideration is given to the pathological aspect of an inflammation of the lung itself—a pneumonia or pneumonitis—and not to the manifestations elsewhere that are a part of the disease that is termed by the clinician pneumonia. Yet we may not, for a moment, disregard the fact that the reader finds his interest chiefly in the clinical manifestations of the disease. It is necessary that one see, at the outset, that an inflammation of the interstitial tissue of the lung is just as truly a pneumonitis as an inflammation of the air sacs, though by no means so common. Even more important is it for him to recognize that, numerous as the causative agents are, and diverse as are the modes of infection, yet the air sacs respond to irritations of all sorts in much the same way. Just as was said in the general discussion of inflammation, the process may vary in speed, in intensity, and now this feature and now that other may be prominent, but at the bottom of them all lie the same fundamental occurrences; the blood vessels become congested, there is an outpouring of serum and a diapedesis of leukocytes, a formation of fibrin, a contemporaneous killing or injuring of the cells of the part, especially those that line the air sac, and even a multiplication of those cells that are mildly

irritated— all this occurring in the closed-in space of the air sac, so that the products of the inflammatory process fill the air sac to the exclusion of air, and the disposal of such products constitutes a step to be performed by the body in the process of healing, over and above what has to be done in a case of inflammation on a surface.

Almost all the known pathogenic organisms have the power of causing pneumonia; the Fränkel-Weichselbaum diplococcus of pneumonia, Friedländer's bacillus of pneumonia, the Streptococcus pyogenes, the Staphylococcus albus and aureus, B. tuberculosis, B. typhi abdominalis, B. coli, B. influenzæ, B. pestis, B. anthracis, and B. diphtheriæ include nearly all. While each of these is able unaided to produce the disease, it actually happens very often that the infection is mixed. As to the manner of infection everyone of these bacilli can reach the lung either by the bronchial tract (**aërogenic pneumonia**) or by the blood or lymph (**hematogenic, lymphogenic pneumonia**). As to what clinical type of disease will be set up by a special organism, we can say little more than that there is no unvarying rule; the pneumococcus sets up most often a lobar pneumonia, but may cause the lobular form, while there seems no reason to suppose that any of these organisms is unable to cause a lobar pneumonia, Be this as it may, lobar pneumonia in the clinical acceptation of the term, is a very different kind of disease from any other form of pneumonia; it is essentially a general blood infection with a local manifestation in the lung; histologically this local manifestation has close resemblance to other pulmonary inflammations.

These pulmonary infections are due, it will be seen, to bacteria, many of which are habitual residents of the body; under what conditions do these bacteria gain power to attack the tissues? Perhaps the body is attacked at a moment of chilling or at a time when resistance is in some other way lowered, or the bacteria become increasingly virulent; the mere fact that a particular lobe is attacked seems to indicate that this is a place of least resistance. Lobar pneumonia is that form in which a part of a lobe, a whole lobe or several lobes are affected; all other forms of pneumonia are of the lobular type in which the unit affected is the lobule. The names by which the different forms are characterized are many, some based upon the mode of conveyance of the causative agent, some upon the anatomical character of the lesion. Among the clinical types of lobular pneumonia are **bronchopneumonia**, in which the infection travels down one or many bronchi, thus obtaining a lobular distribution; **miliary pneumonia**, in which the blood stream infects multiple foci at once; **septic** and **metastatic pneumonia**, in which the lung is affected in multiple areas as an expression of a widespread bacteriemia; **hypostatic pneumonia**, in which the lobules attacked are necessarily in areas that are already the subjects of passive congestion, and **terminal pneumonia** in which the lung is attacked because it, in common with the rest of the body is in a low (ante mortem) state of resistance. All these have a lobular distribution of the infection. While the character of the

Fig. 278
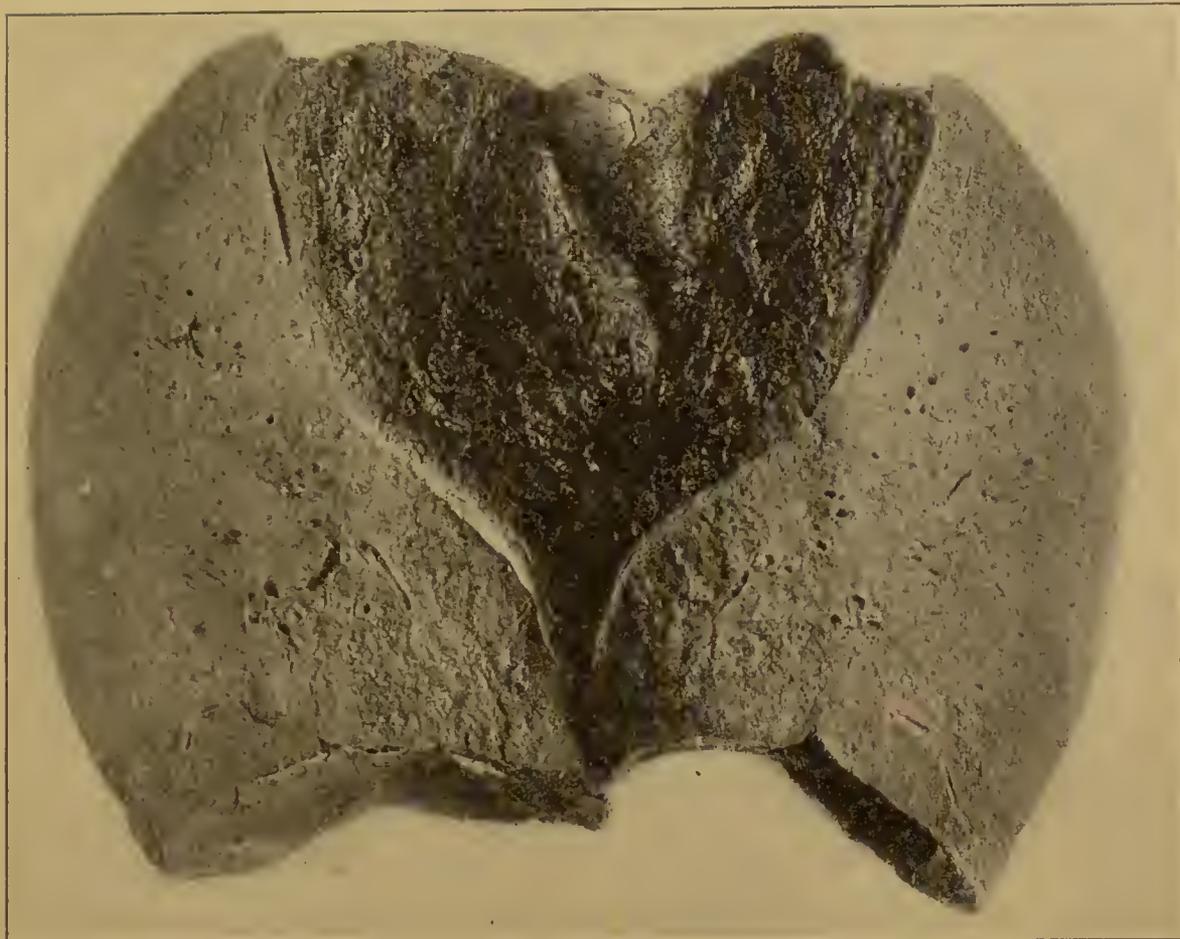
Acute lobar pneumonia (gray hepatization). The lower lobe is involved. (Pathological Museum, McGill University.)

Fig. 279

Lung; acute lobar pneumonia, stage of red hepatization. The centre of the microscopic field is occupied by an air vesicle containing a mass of exudate composed of a network of fibrin, red blood cells, and a few leukocytes. (Hare.)

exudate may sometimes enable us to decide what is the infection, our knowledge of the process of inflammation will render us cautious as to depending absolutely upon this, and the smear and the culture are safer means of differentiation.

Acute Lobar Pneumonia.—The well-known division of the course of the disease into four stages was never accurate and has outlived its usefulness. It is clear enough that congestion is followed by consolidation; the lungs seen at autopsy frequently present an appearance well described in the term "red hepatization," often show the state of gray hepatization, and very often are seen in a moist, gray state well described by the term purulent infiltration.

The period of **congestion** or **engorgement** is undoubtedly brief, rarely seen by the pathologist and often referred to by careless clinicians as "congestion of the lungs," "threatening pneumonia," or some such term. What the clinician can observe at this stage is merely the moist state of the bronchi and bronchioles; considering the frequency of bronchitis, all the preliminary signs of the onset of pneumonia are required before he may make even a likely guess as to whether pneumonia is or is not to supervene. The lung at such a time is reddened, distinctly œdematous; if seen at autopsy it oozes abundant blood on section and is curiously brittle. This quickly gives place to consolidation, in which the lung becomes heavy, swollen, firm, pits on pressure, and is more friable than normal. It is intensely red, owing to vascular hyperemia rather than to the presence of red corpuscles in the exudate, and the fluid scraped off the cut surface with a knife is definitely turbid, and blood-stained. Microscopically, the capillaries are congested, the lining epithelium of the air sacs is swollen, often desquamated, and fibrin and leukocytes are present, the fibrin threads making a complete mesh in the air sac just as a blood-clot adheres to the sides of a glass vessel. Red corpuscles are present. From the red solid appearance of the tissue in this state, it was likened to liver, and the term **hepatization** applied to it. To understand properly how this changes to the so-called **gray hepatization,** a consideration of the microscopic appearance is necessary. After the lapse of a little time the fibrin threads begin to break up under the action of enzymes, and just as the blood clot shrinks away from the sides of the glass vessel, so the exudate or clot shrinks from the sides of the air sac and microscopically a clear zone (actually filled with serum) appears around the exudate; the fibrin is now being digested, dead cells are being disintegrated, and the "scavenging" effect of leukocytes and proliferated air sac cells becomes apparent; leukocytes are now present in so great numbers that the tissue takes the characteristic color of lymph tissue—gray; disintegration of the exudate proceeds, until the air sac contents become thinner and thinner, until there remains only lymph, which is absorbed, and air once more enters the air sac. Or it may be that the loosened plug of partly disintegrated exudate is suddenly dislodged by a cough into the bronchiole, and appears in the sputum, where we

can recognize the fibrin, the leukocytes, the desquamated epithe-
lium and the bacteria. This disintegrating stage, with its num-
erous leukocytes is that of gray
hepatization. The surface is
granular, gray in color, the lung
is firm, probably indented by the
ribs, the pleura is no longer glassy
but dulled by a fine fibrinous
exudation, the lung is airless,
friable and sinks in water. The
cut surface looks granular, and
scraping yields a fluid no longer
blood stained, but more turbid
than ever. As time elapses, the
disintegrative process goes on, the
lung losing its firmness, the surface
becoming more lax, and the stage
of gray hepatization has definitely
passed into that of **resolution**.
Many cases, however, do not ex-
hibit this course, but appear at the
death of the patient in a state of
"purulent infiltration," which dif-
fers from that just described as
gray hepatization only in this—
that the lung is more moist, and

Fig. 280

Section from a lung with acute lobar pneumonia
in the stage of gray hepatization. All the fibrin
here has been disintegrated: *a*, desquamated
alveolar cell; *b*, disintegrating leukocyte; *c*,
normal leukocyte.

the scraped surface, granular for an instant, quickly becomes clouded
over by a thin layer of fluid pus which exudes from the alveoli and
bronchioles; the tissue is even more friable than before, because the
alveolar septa have undergone a considerable degree of disintegration.
One can well imagine that, had life been prolonged, the entire affected
area would soon have become one large abscess.

As to the site of the pneumonic process, our own figures show the
right side affected in 48 per cent., the left in 30 per cent., and both in
22 per cent. of cases. When both lungs are affected it is common to
find one farther advanced in the disease than the other. The lower
lobes are more often the seat of the disease than the upper, but it is
not infrequent to find atypical forms such as **"apical," "central,"** and
"creeping" pneumonia, terms which explain themselves.

Considering the nature of the disease, viz., that it is a generalized
infection, it is to be expected that the infection in the lungs may be
associated with inflammation elsewhere; pleurisy, empyema, peri-
carditis, endocarditis, meningitis, osteitis and arthritis are those of
commonest occurrence.

Instead of proceeding to resolution, the exudate may remain in the
alveoli and organize (as might a clot elsewhere), giving rise to the rare
instances of unresolved pneumonia. It is a good clinical rule to remem-
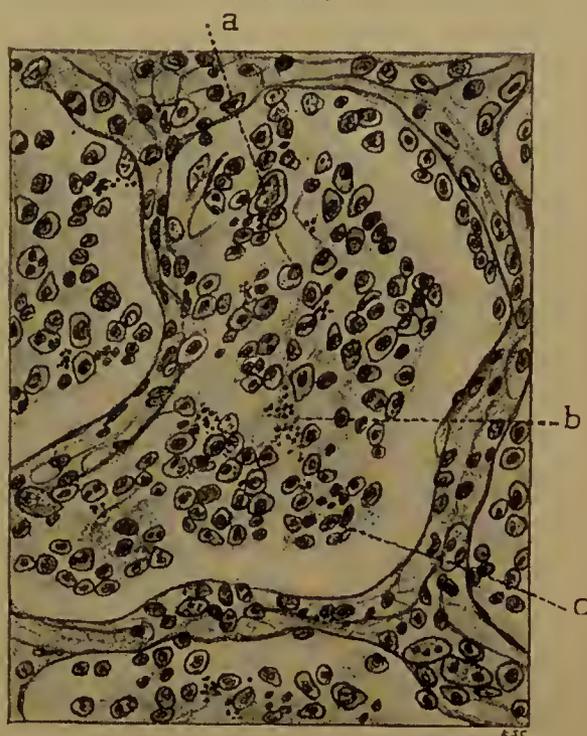
35

ber that this is one of the least common causes of continuance of the pneumonic febrile state, and he who keeps the figures of frequency of occurrence in his mind will wisely dispose of other possibilities, especially empyema, before coming to this diagnosis. Secondary infection may lead to a breaking down of the lung tissue causing abscess or gangrene, closely related conditions. Especially if putrid bronchitis or bronchiectasis have been present, is gangrene apt to supervene, the lung becoming pulpy, greenish in color, and stinking. A line of demarcation rarely exists, and irregular cavities with shaggy, necrotic walls are seen. Even this may heal by a fibrosis, the part of the lung affected finally shrinking to a dense, indurated mass.

FIG. 281

Two alveoli from the lung in acute lobular pneumonia, showing looser cell collection in the exudate and absence of fibrin: *a*, disintegrating leukocytes with granular contents; *b*, same with fat globules.

Acute Lobular Pneumonia.—Only rarely is this a primary disease, save in young children; it is usually the sequel to bronchitis or one of the infectious fevers, measles, whooping cough, influenza, or diphtheria, and the young, the old, or the debilitated are the sufferers. The organisms are the same as in the lobar form, but the pyogenic cocci have a greater tendency to be concerned. A bronchial inflammation that has spread to the bronchioles is very certain to go a short step farther and attack the air sacs. It is all but a safe statement to make that the exudate is more serous than fibrinous, and a striking feature is the presence of large, clear, mononuclear cells, which are, in all probability, the swollen alveolar cells, and these give to the exudate a "catarrhal" quality.

Coming from the bronchi, this disease is apt to attack both lungs,

although only one or a part of one may be affected. The damaged lung is congested and in its substance are isolated firm areas, raised above the rest of the surface, gray, red, or yellow in color, and friable in consistence. These scattered areas may grow larger till they coalesce, but they never succeed in producing the uniform solidity of the lobar type of pneumonia. With the possible exceptions noted above, a piece from the middle of one of these areas is microscopically indistinguishable from a similar piece cut from the middle of a lung in lobar pneumonia. The individual consolidations pass through red and gray stages, and the sporadic distribution of these areas has led to the lung being likened to a spleen—hence the term **"splenization"** (not to be commended). When consolidation occurs and resolves, the resolution is apt to progress more quickly than in lobar pneumonia, because the lymph and blood streams are less interrupted, but not the less is it a serious disease, since it attacks at a time of low vitality or complicates other grave disease. Several of the different forms must be considered individually.

Aspiration Pneumonia.—A typical example of lobular pneumonia is that known as **inhalation** or **aspiration pneumonia**, arising from the aspiration of food, vomitus, or secretion from the nose and mouth during unconsciousness, as in the anesthesia of operations. From the nature of the infecting agent it will be readily understood that the tendency to destruction of the lung tissue, to abscess, and gangrene is greater than usual. It is a frequent occurrence that in surgical cases ending fatally, especially where vomiting has been present, the trachea and bronchi show a greenish tint, suggesting bile-stained stomach contents, and this usually indicates that such have been aspirated. Where life is sufficiently prolonged to allow the pneumonic process to supervene, the profuse sputum, often fœtid, shows by the presence of elastic tissue that the lung tissue is being destroyed, and at autopsy scattered or confluent areas of actual abscess formation will be found; the zone surrounding such areas is likely to show a very intense congestion because seen in so vascular an organ. Septic pneumonia may be caused in other ways than by inhalation; the extension of inflammation from neighboring tissues, such as the mediastinum or from subdiaphragmatic structures, will cause it, as may also infection at the time of injury to the lung as in perforating wound of the lung through the chest wall. Wound of the lung by a rib, where no external wound exists, is more likely to be followed by an unmixed infection and a typical pneumonia, because the wounded area is the place of least resistance for the time being, and the infection is hematogenic.

Metastatic or Embolic Pneumonia.—This is allied to the last form. It happens as a manifestation of a general bacteriemia in such diseases as osteomyelitis, thrombophlebitis, arthritis, septic endocarditis, and erysipelas, where a septic embolus becomes the point of origin of a pneumonic focus. No part of the lung is exempt, and the abscesses

can be felt as indefinite lumps deep in the tissue or seen as yellow swellings under the pleura, varying in size from that of a pinhead to several centimeters in diameter. The inflammation set up by the septic material brought by the embolus, although circumscribed, is of the nature of a localized pneumonia, but it proceeds straightway to the formation of abscess or gangrene. Of pneumonic nature, strictly speaking, is also the effect of secondary infection in tuberculosis, actinomycosis, or other primary infection.

Hypostatic Pneumonia.—A pneumonic infection occurs very often in those who are debilitated, and because the posterior parts of the lungs are congested and œdematous it is here that the infection strikes, and a diffuse catarrhal pneumonia, definitely localized to this part of the lung, is set up; the general bodily depression has much to do with the infection, for it is known to every clinician that lungs may remain congested and œdematous for months without infection; but when the individual comes within a few hours of his death, the so-called terminal infection takes hold, and thus it is that so many patients suffering from heart disease die *with*, if not *from* a pneumonia.

Chronic Pneumonia.—Care is necessary in considering chronic pneumonia not to include the actual reparative process that may follow an acute pneumonia, unless an actual lesion of the alveolar septa occur. The term chronic pneumonia presupposes that an irritant is continually and progressively at work. An **"unresolved pneumonia"** is correctly a chronic pneumonia, and the infections of the granulomas, tuberculosis, syphilis, actinomycosis, etc., set up an inflammation that may be so designated. Chronic pneumonias may be divided into (1) the above-mentioned **secondary indurative pneumonias**, (2) **pneumonokonioses**, the diseases excited by the inhalation of various kinds of dust, and (3) **pleurogenetic pneumonias**, caused by the extension inward of the infection of a chronic pleurisy, a rare form.

1. *Secondary Indurative Pneumonia.*—There is a general substitution of fibrous tissue for the soft lung substance, the pleura and interlobular septa being specially prominent. If it occur secondary to a bronchopneumonia, the fibrosis roughly follows the bronchial tree. In an advanced case, seen microscopically, one is struck by the fact, that, whereas normally the greatest part of the section is air space, and the least the walls, here the greater part of the field is solid tissue and the lesser part is air space. The lung is heavy and hard, cuts firmly, is grayish in color, mottled with the black of inhaled dust. Areas of necrosis resembling caseation may be seen, the pleuræ are thickened and often matted together, and the lung may be entirely deformed. Microscopically, the air sacs show as small irregular spaces containing desquamated cells or leukocytes, lined by irregular cubical cells, and separated from one another by wide masses of fibrous tissue. The bronchi are irregular in shape from pressure or traction. Now and then in the fibrous tissue one sees large collections of leukocytes and young fibroblasts indicating areas of acute inflammation in the fibrous

tissue, where some infection still continues to operate. This extreme grade of change never follows passive congestion; here, at the most, there is moderate thickening of the septa and the alveoli show many catarrhal cells containing pigment (**brown induration**).

FIG. 282
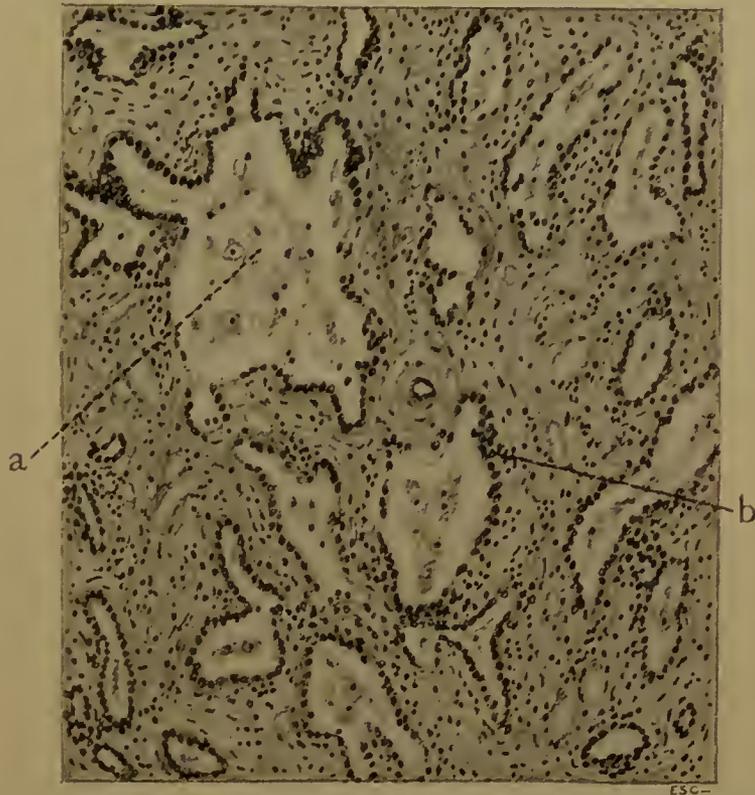
Section from a case of indurative pneumonia (fibrosis of the lung), showing the extreme fibroid thickening of the alveolar walls and the consequent reduction in size of the alveoli: *a*, alveolus containing desquamated cells; *b*, somewhat cubical epithelium lining the air spaces.

2. *Pneumonokoniosis.*—Little, if any, inhaled dust reaches the air sacs directly in the air, but it impinges on the bronchial walls, is carried by the leukocytes and endothelial cells to the peribronchial lymph collections or to the alveolar walls. Wherever it lands it may set up a certain amount of irritation, the more so if its particles are sharp-edged, because these actually pierce the walls and set up in the surrounding tissues nodular reactive growths, like tubercles, in which the offending particles are shut up. In advanced cases the peribronchial lymph nodes may be gritty, and particles may be carried to the abdominal lymph nodes. Different kinds of dust set up different degrees of irritation; the most familiar form is **anthracosis**, from coal dust, found in all adult dwellers in cities, and unimportant; in the case of coal-miners, however, the damage wrought may be great, and anthracotic tubercles are seen as grayish masses of fibrosis with black centres, while the entire lung is somewhat infiltrated and is heavy. In the stone-mason's lung (**chalicosis**) the infiltrating material is grey and gritty; in **siderosis** particles of iron and steel do the damage, as is seen among needle-grinders, file-makers, and iron-workers of different kinds.

The lesions are not very different from those of indurative pneumonia; calcification and even the formation of bone have been seen.

Tuberculosis.—Tuberculosis occurs in the lungs both as an acute and a chronic disease, the Bacillus tuberculosis, discovered in 1882 by Koch, being the essential agent.

As to the mode of infection, it may be stated that tuberculosis is not hereditary, and but few cases of intra-uterine infection are known to have occurred. As to how the organisms reach the lung there has been much debate; a reasonable statement of the facts seems to be the following: the infection of the lungs is nearly always by the human type of organism; the bovine or the human form may be ingested with food and may be carried by the lymph stream ultimately to the thorax and infect the lungs, although this is probably an infrequent happening. Most pulmonary infections occur by inhalation; of these very few are direct, that is, result from the bacilli being engrafted upon the bronchial surface and setting up a tuberculous bronchitis as a primary lesion. The bacilli are usually caught in the mucous membrane, carried to the lymph nodes where the infection may remain (and be subsequently transferred by the lymph stream to the lung), or they may be carried at once by the lymph to the lung. This transference may also occur by the agency of the blood; and cases in which a tuberculous area in a lymph node breaks into a bronchus, a bronchiole or a blood vessel are so obvious as not to require explanation. This last is an unimportant fact, for it happens oftenest in advanced cases. Infection by the skin, especially by the bovine form of the bacillus, happens, though rarely.

Viewed broadly, the greatest dangers to which people are exposed arise from the inhalation of dried sputum or exhalation from the mouth and nose. Personal contact constitutes a grave danger, but being foreseen may be guarded against; the infection of houses and rooms, and their subsequent occupation by those who are ignorant of the fact, is a great source of risk, and can be obviated only by rigid regulations compelling notification of cases, inspection, and disinfection of houses. Tuberculous milk, butter, or meat is no more serious menace to the public health than the existence of unmarked contaminated houses and rooms.

From the above considerations it will be seen that, according to the generally accepted views of the present time, pulmonary tuberculosis instead of being primary is, in the majority of cases, truly secondary, and of hematogenic or lymphogenic origin, although the mode of infection is in the first place aërial. Some authors go so far as to say that all infections occur in early life, and that the bacilli are stored up for long periods of time in the lymph nodes.

Aërogenic Tuberculosis.—Wherever the bacilli, carried as above stated, lodge in a part of the lung suitable for their growth, they result, according to how numerous and how virulent they are, in a simple tubercle or a small localized area of the nature of a lobular pneumonia. The site of predilection is just below the apex where the excursion of the

lung is slight and gaseous interchange slow, or otherwise, however extensive their distribution throughout the lung substance, they tend to

Fig. 283
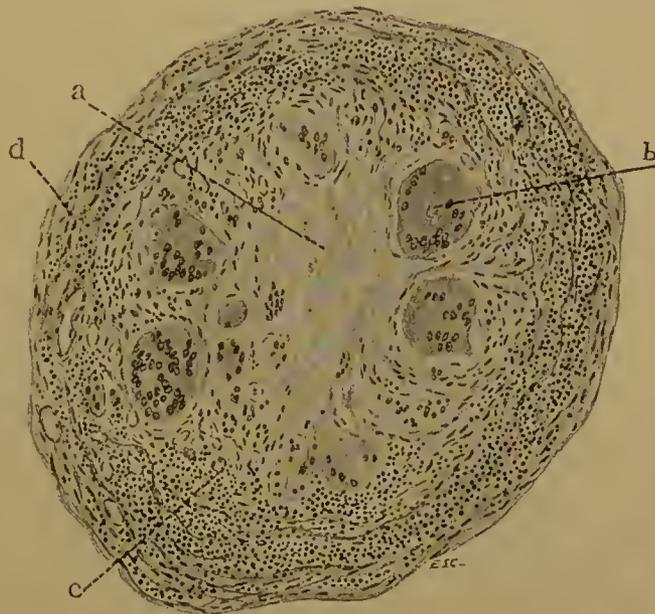
Tubercle from a case of tuberculosis, of medium severity, of the lung: *a*, central caseation; *b*, a giant cell; *c*, endothelial cells; *d*, connective-tissue zone infiltrated with lymphocytes.

Fig. 284
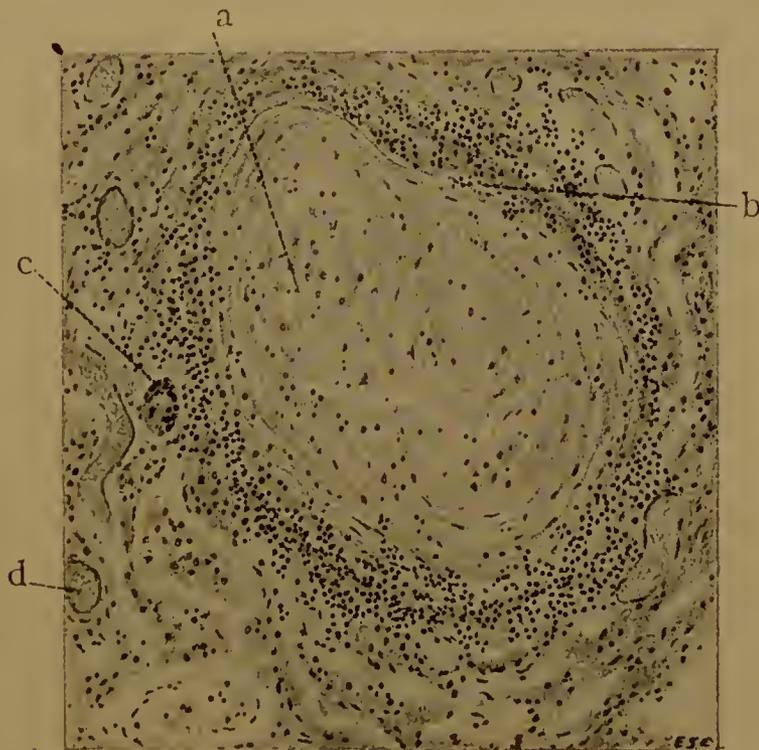
Section through early apical tubercle, showing: *a*, central caseation; *b*, surrounding cellular infiltration with fibrosis; *c*, giant cell; *d*, congested capillary outside tubercle, the tubercle itself being devoid of vessels.

grow only in the region or regions of least resistance. Clinically, it will be recalled that if a lesion be found in one apex it is well to search carefully the other apex, and then the apex of the lower lobe of the lung

first involved. At first the area involved is small, gelatinous in appearance and imperfectly differentiated from the surrounding tissue. The only physical sign available at this time or even for some time to come may be fine rales in the moist bronchioles of the region. A cellular exudate is thrown into the alveoli, and the vessels become blocked by endothelial proliferation, caseation quickly ensuing. The sharply defined lesion now existent, may even yet heal, and be represented by a fibrous scar, or a fibrous mass with caseous or calcareous centre, and a puckering of the apex of the lung. If, however, the process continue, the bacilli are carried by the lymphatics and secondary similar foci arise on the periphery of the first. The nodules gradually increase in size and coalesce, the caseation increasing with equal pace, until the caseated areas in turn coalesce. The nearby pleura and the lymph

FIG. 285
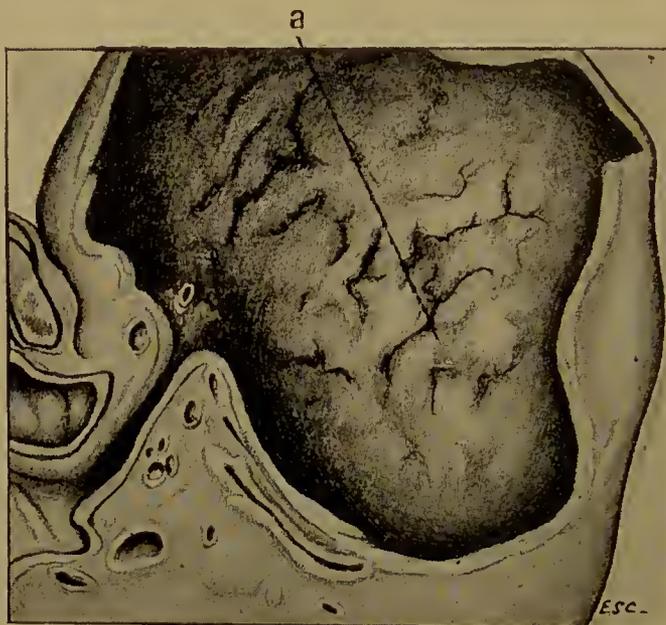
Tuberculous cavity (a) at apex of lung, showing its relation to a bronchus. (Pathological Museum, McGill University.)

nodes become likewise infected. Presently a bronchus is invaded which gives outlet to the broken-down caseous material, and bacilli appear in the sputum, contemporaneously with the formation of the first cavity. A gradual progression of infiltration and overgrowth of tissue in any or in all directions is now followed by the corresponding breaking-down process, so that the whole routine is repeated on an ever-increasing scale of size. The cavities may fill and refill with fluid exudate; if a secondary infection of their contents occur, the process becomes more freely suppurative and in most cases more active. The walls are ragged and fibrous and may be lined by a typical "pyogenic membrane." Most resistant, the septa and the blood vessels may be left bridging the cavity, and when the latter are eroded or form small aneurysms and break, hemorrhage occurs. Hemorrhage may occur in the most minute cavity and thus may be the first symptom to be

observed. When a cavity opens into a bronchus and discharges its contents, it is likely that not all the latter will be expelled, but they may be aspirated elsewhere and set up a **tuberculous bronchopneumonia** in the tissue nearby. Should the infective agent in this material be the tubercle bacillus, the resulting pneumonia will be truly *tuberculous,*

Fig. 286
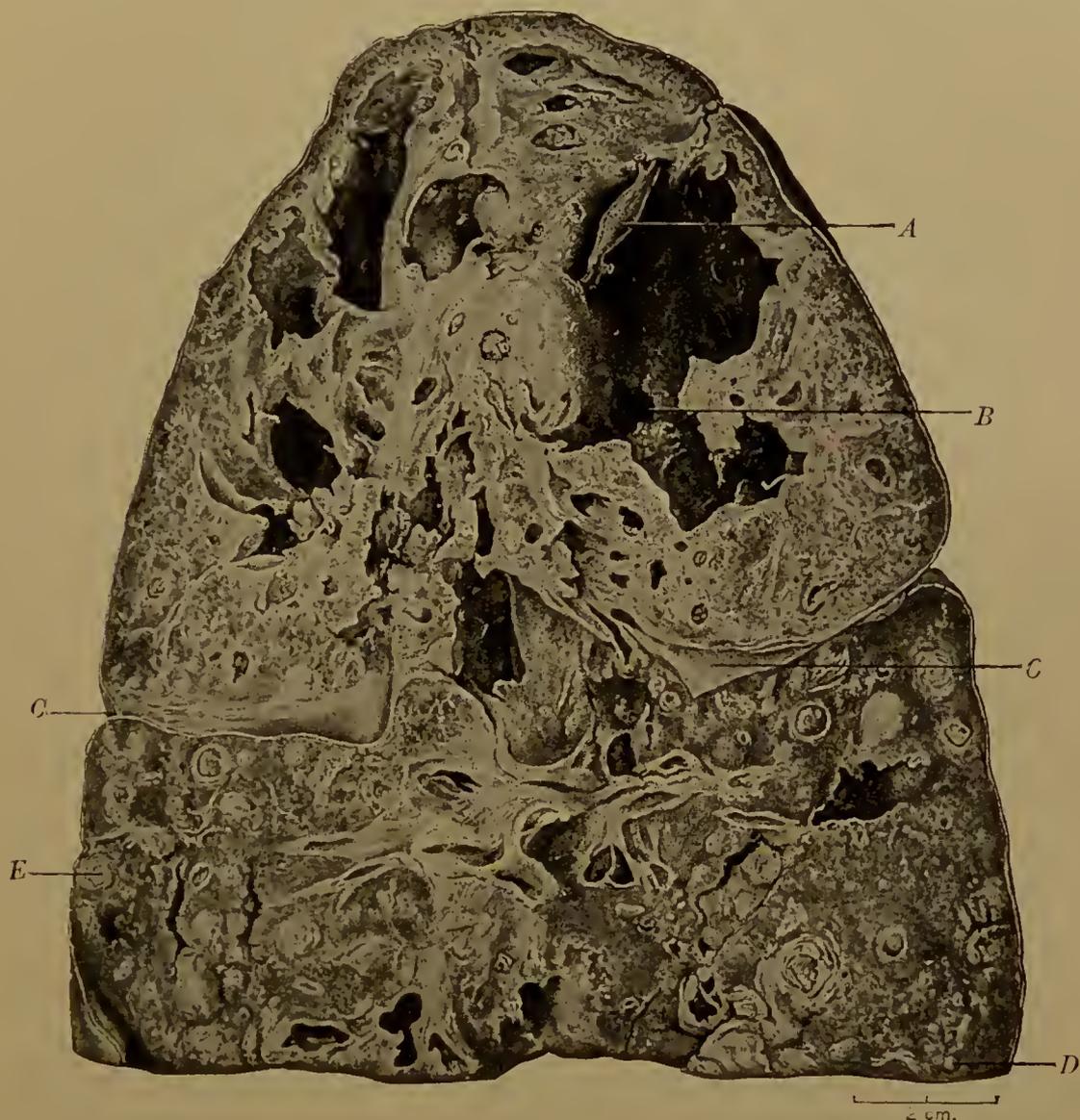
Left lung, superior lobe, and upper part of lower lobe, the former containing a number of communicating caverns, brought about by tuberculous infiltration, caseation, and evacuation of the contents through the bronchi: *A*, aneurysmal dilatation of an artery spanning one margin of a large cavity; *B*, communication with another cavity; *C, C*, thickened and adherent pleura between the two involved lobes. The pleura over both lobes is thickened, and at the autopsy the cavity had been obliterated by universal adhesion; *D*, a small group of tubercles in which caseation is just beginning; *E*, a fused group of tubercles, farther advanced that at *D*. (Hare.)

but if pyogenic cocci be present, they may set up pneumonia, strictly bronchopneumonia in a tuberculous lung. It does not greatly matter which is the case, so far as the patient is concerned. Such an infection, if tuberculous, may give origin to a bronchitis in which tubercles form in large numbers along the bronchial tree and subsequently coalesce, so that large caseous masses may be produced, each surrounded by a zone

of simple pneumonia. The avascularity of such a large caseous mass is of importance in that the breaking-down process goes on the more rapidly. Seen post mortem, the lung is generally adherent to the thoracic wall, weighty, the upper lobe largely caseous with multiple cavities, while caseous nodules are scattered through the rest of the lung, the largest in the lower lobe being usually at its apex. Variously sized cavities may exist, or the upper lobe may be converted into a thin-walled bag containing air, pus, caseous matter, detritus, and occasionally blood. The more chronic the process, the more smooth and fibrous are the walls. The bronchi are inflamed, often ulcerated, and usually communicate with some of the cavities, which often communicate with one another. This state of the lung is called **chronic ulcerative tuberculosis** or **phthisis**.

The above-described process is frequently seen; other rarer types of tuberculosis are described under many different names which are rarely used in a uniform fashion. Without going especially into this part of the subject it may be said that all are permutations and combinations of three original kinds of reaction: (1) the individual tubercle, (2) small or large coalesced areas of tuberculosis with caseation, and (3) tuberculous lobular pneumonia. Most cases of the disease at autopsy show all three; now one form of reaction is more prominent clinically, now another. There are two forms frequently referred to which require mention: "galloping consumption" and "fibroid phthisis." "Galloping consumption" or **acute pneumonic phthisis** is a term apt to be applied carelessly to any form of pulmonary tuberculosis that runs a very acute course, but should not be used to describe the generalized hematogenous miliary type of the disease; it is characterized by a widespread caseous pneumonic state of a lobe or a whole lung—is, in fact, a combination of caseous tuberculosis and pneumonia, the lesion looking microscopically like the former and the involvement resembling that of the latter disease. "Fibroid phthisis" is merely a very slowly progressing ulcerative tuberculosis, in which there is ample time and stimulus for a marked degree of protective fibrosis to occur. The fibrous solidification of lung tissue, with its contraction and consequent deformity of the lung and even of the chest are the striking features of this type of tuberculosis.

Hematogenic Tuberculosis.—This form of the disease is characterized by the dissemination of the bacilli by the blood either in the lungs alone, or in the lungs in common with all the organs of the body. A caseous focus breaking into a vessel or into a large trunk of the lymphatic system is the usual cause, and the widespread occurrence of tubercles in so many foci at once brings it about that death occurs before any considerable degree of enlargement and caseation occurs in any one of them.

The lung so affected is hyperemic, heavy, and the tubercles are felt, or later seen, as shotty, granular particles in enormous numbers in the tissue, throughout both lungs in the generalized disease, in one

or a part of one in the local forms. The bronchi are reddened. From the small size of the tubercles (Fig. 288) each has been likened to a millet seed (*milis*) and the term **miliary** has been given to them. Tubercles of the same small size and miliary appearance may also at times be encountered as the result of bronchogenic, not hematogenic infection; in such a case their arrangement is not uniformly diffuse; they occur in little grape-like clusters along the course of individual bronchi.

Fig. 287
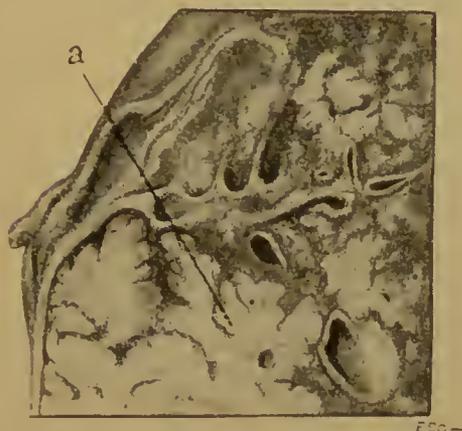
Caseous tuberculosis (*a*) passing on to caseous pneumonia. (Path. Mus. McGill Univ.)

Fig. 288

Hematogenous miliary tuberculosis of lung. (Path. Mus. McGill Univ.)

Lymphogenic Tuberculosis.—Infection of the lungs may occur from a tuberculous caries of the spine or rib, and occasionally by direct extension from a lymph node; the most frequent example, however, is the secondary spread of the disease in the lung itself. Under this heading it may be pointed out that there is still debate as to the part played by the pleura and its lymphatics in the origin of apical tuberculosis. It is held by some that the pleural cavity becomes infected from the lower cervical lymph nodes, and that, from this, infection most easily involves the apical region of the lung.

Syphilis.—Syphilis of the lung is rare, and is seen oftenest in the newborn. No doubt some cases considered as syphilitic bronchitis and pneumonia are merely instances of a mixed infection occurring in syphilitic subjects. The disease proper manifests itself as an **interstitial fibrosis** or as **gummas**. Gummas are rare, found oftenest near the hilus, and if healed may leave a fissure forming a false lobe (**pulmo lobatus**). Grayish, translucent when small, gummas may in their later stages appear very like tubercles. The diffuse interstitial form is due to a general widespread infiltration by inflammatory products that can be readily understood by anyone who has seen the enormous numbers of spirochetes that infest the lung. The anemic pallor of the organ has led to the condition being described as **white pneumonia.**

Actinomycosis.—Streptothricosis (see p. 234) occurs in the lung both as a primary and a secondary infection, conveyed from the mouth by

inhalation, or by extension from the mediastinum or œsophagus. Sometimes manifest as miliary nodules, it may, nevertheless, set up a bronchopneumonia and consolidation with cavitation may be found. If very chronic and long continued a fibroid lung may result.

Fig. 289
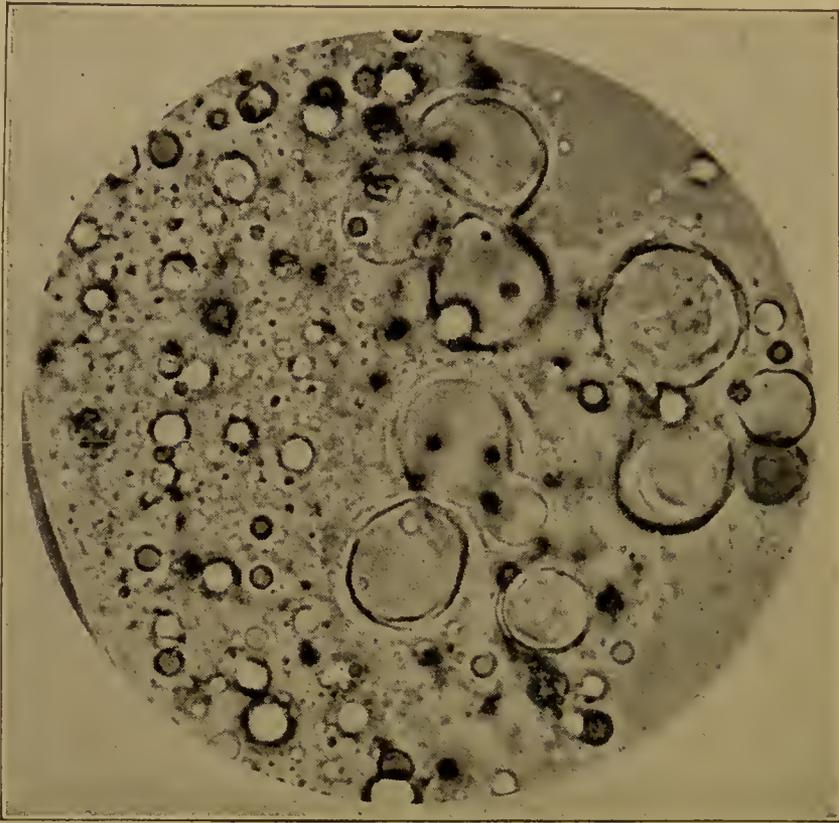
Blastomyces from sputum. Some of the individuals are in the budding state. The small circular objects seen are droplets. Oil immersion. (Eisendrath and Ormsby.)

Glanders.—Like actinomyces, the B. mallei may set up an acute pneumonic process or a chronic state characterized by multiple miliary nodules, hardly to be diagnosticated except by the discovery of the bacillus.

Various Infrequent Infections.—There are certain organisms that have been found infecting the lung, capable of setting up either caseating granulomas or diffuse pneumonia or abscesses. **Cladothrix, streptothrix, blastomyces** (Fig. 289), some of the **hyphomycetes, aspergillus,** and even animal parasites, such as **strongylus** and **distomum Westermanni,** have been found. **Echinococcus,** carried from the liver, may form cysts in the lungs as elsewhere.

Regressive Changes.—We have already spoken of the atrophy of the lung seen in emphysema (see Fig. 271, page 523). Here we would merely recall that this emphysematous process is often secondary to a progressive atrophy and disappearance of the elastic tissue of the lung. The chronic deposit of fibrous tissue around the arteries and the bronchi seen in the old, the so-called **periarteritis** and **peribronchitis,** is,

as the names imply, usually regarded as an inflammatory condition. It is perhaps more properly considered as a progressive than a regressive change.

Progressive Tissue Changes.—Hypertrophy may be said not to occur in the lung, increase in size being emphysematous, not hypertrophic. Tumors of primary nature are rather rare; of benign growths **fibroma, lipoma, chondroma,** and **osteoma** are found, the last named not to be confounded with the metaplastic formation of bone previously mentioned; **adenoma** and **teratoma** are of great rarity. While the lung is a common site for secondary malignant tumors, especially those carried in the blood stream, primary malignant tumors are not very common. **Sarcoma** is found arising from the lung tissue, **lymphosarcoma** from the lymph tissue, especially at the root of the lung, and **endothelioma** from the lining of the lymphatics or from the pleura. Primary **carcinomas** may originate in the bronchial or the alveolar epithelium or in the peribronchial mucous glands, and are important from the frequency with which they project into and block the bronchi, with resultant collapse of the lung tissue. Metastases of tumors that produce secondaries appear with fair frequency in the lung, especially the **chorioepithelioma,** whose tissue of predilection it is.

THE PLEURÆ

The pleuræ are sacs composed of a thin, loose, connective-tissue membrane containing numerous blood vessels and elastic fibrils and covered by a single layer of flattened endothelial cells. These sac-walls being normally in perfect apposition, the pleural cavities are non-existent. Any content, therefore, constitutes an abnormality. Not very prone to primary disease, they often suffer by the contiguity of the lungs, and by the relatively free lymphatic communication with the pericardium and the peritoneum. The course of any disease of the pleura is influenced by the constant movement inseparable from respiration.

Circulatory Disturbances.—**Hyperemia.**—**Active** hyperemia occurs in inflammatory affections and with congestion of the lung proper, and occasionally from relaxation of tension when thoracentesis has been performed, while **passive** hyperemia is found in obstruction to the greater or lesser circulation.

Hemorrhage.—Petechiæ, ecchymosis, or even gross hemorrhage may arise from trauma, in suffocation, in renal and cardiac disease, in severe infections and intoxications and in instances of the hemorrhagic diathesis.

The Existence of Contents in the Pleuræ.—**Hematothorax.**—Blood may be effused into the pleural cavity in wounds of the chest such as fracture of the ribs, involving the pleura, or by the bursting into it of an aneurysm, in which cases the blood may be unmixed. Often,

however, it is mixed with transudate or some product of inflammation, as in the case of certain forms of pleurisy, with new growth, or when a tuberculous or gangrenous cavity ruptures into it.

Hydrothorax.—This consists of the presence of a transudate in the pleural cavity, occurring oftenest on the right, frequently on both sides. The explanation offered for its greater frequency on the right is that a distension of the right side of the heart presses upon the veins of that side. Pleural adhesions may localize the fluid to a part of the cavity affected. The fluid is usually pale, straw-colored, alkaline, of a specific gravity of 1009 to 1012, containing 2 to 5 per cent. of albumin; microscopically it contains nothing but accidental leukocytes and desquamated endothelial cells. The surface of the pleura remains smooth but in long-standing cases becomes thickened and even pearly by reason of overgrowth of the fibrous tissue.

A small amount of fluid may transude into the pleura during the death agony, but plentiful transudations are found in nephritis, broken compensation of the heart, cirrhosis of the liver, hydremia, and pulmonary œdema. A small collection of fluid is of little significance, but the larger ones lead to displacement of the heart, mediastinal structures, and lungs.

Chylous Hydrothorax.—This consists of an admixture of the fluid with fat globules, granular material, and lymphoid cells, rendering it opaque and whitish, and is caused by a rupture or obstruction of the thoracic duct above the point where it enters the thorax.

Pneumothorax.—This is the term used to designate the presence of air in the pleural cavity. By reason of the nature of the exciting causes, there is usually inflammation present and the cavity contains not only air but also serum (**hydropneumothorax**), or pus (**pyopneumothorax**). Mechanically it may be produced by a penetrating wound of the chest, even by thoracentesis; most commonly it follows the rupture of a tuberculous or gangrenous cavity through the pleura during a severe paroxysm of coughing; an empyema may rupture into the lung, or air (or gas) may come from the œsophagus, stomach or bowel previously rendered adherent to the pleura or to the pleura and diaphragm by new growth. Certain varieties of pneumothorax may be differentiated: (1) **open pneumothorax**, in which air passes freely in and out, (2) **valvular pneumothorax**, in which an oblique, valve-like opening allows air to enter but not to escape, (3) **closed pneumothorax**, in which the opening has become occluded, and (4) **artificial or surgical pneumothorax** in which nitrogen or other gas is conveyed to the pleural sac for the purpose of compressing and giving a greater than normal degree of rest to a diseased lung. Pneumothorax, without perforation, can occur in the event of an infection of the pleura by a gas-producing organism.

The effect of pneumothorax depends upon the cause and the persistence of the communication with the outside; while the fistula remains, the lung will be collapsed unless prevented from so doing by adhesions. Where a valvular opening is present the cavity becomes

more and more distended until the heart is pushed over and the diaphragm depressed; if there be no infection, and the wound be closed, the air may be gradually absorbed and the lung may resume its natural state.

Inflammation. — Inflammation of the pleura (**pleurisy, pleuritis**) is usually set up by extension of infection from an organ nearby or as a metastatic affection, part of a general disease, as is seen in bacteriemia, rheumatism, typhoid, or the exanthems; practically always bacterial, the disease may be complete or partial, and is either **exudative** or **productive**; the exudative form may arise in a pleura already the seat of a productive inflammation or the exudative form may develop into the productive. These two forms are really expressions of a more and a less acute infection.

Exudative Pleurisy.—The exudate, which here is shut in, unable to escape, may manifest many different appearances; it may be fibrinous (**plastic pleurisy**), serous, serofibrinous, fibrinopurulent, purulent, or hemorrhagic.

Fig. 290

Section from a case of serofibrinous pleurisy (high power): *a*, congested and infiltrated subpleural lung tissue; *b*, fibrous layer of pleura also infiltrated and devoid of endothelium; *c, c*, denser bands of fibrin; *d, d*, loose meshwork of fibrin, infiltrated with serum and leukocytes.

Fibrinous Pleurisy.—In this, the so-called "dry" pleurisy, the pleura is opaque, and covered by a delicate layer of fibrin which scarcely resists removal. This consists of interlaced threads of fibrin, with leukocytes, and bacteria; the vessels of the subjacent lung and of the pleura are congested, and fibrin may be seen in the tissues, which are œdematous and show a certain amount of cellular infiltration.

Serofibrinous Pleurisy.—Few pleurisies remain dry, and there is usually an outpouring of fluid into the cavity (**pleurisy with effusion**); this fluid is yellowish, and if mixed with many cells and shreds of fibrin, turbid. In the dependent parts of the cavity and sticking to the walls of the pleural cavity are shaggy masses of fibrin, bright yellow, sometimes gelatinous, and at times so thick as to form a regular blanket which it requires some force to tear. The amount of fluid may vary from a few cubic centimeters to several liters, it coagulates readily with heat and sometimes spontaneously on removal; its specific gravity is high (1025 or more) and it contains much albumin as well as some uric acid, cholesterin, and sugar. Microscopically, it shows fibrin, leukocytes, red corpuscles, endothelial cells, and bacteria. The condition of the lung varies with the amount of fluid; it may be almost completely collapsed, the heart displaced, and the diaphragm (and with it the liver) depressed. The collapsed part is tough, gray, or grayish brown, or even bluish in color, and is non-crepitant. If not held by adhesions, the fluid moves with the patient's change of posture. When healing occurs the fluid is gradually absorbed by the lymphatics, the fibrin breaks up, and no sign of trouble may remain except a slight thickening of the pleura. Oftener, however, some organization of the fibrous layer occurs, so that the visceral and parietal layers of the pleura remain adherent. With the lapse of time, the adhesions, being constantly pulled upon, become thin and veil-like; such adhesions are often seen between lobes and on the posterior surface of the upper lobe, and in some cases the pleural cavity may be entirely obliterated.

Purulent Pleurisy (Empyema).—This may arise from a serofibrinous pleurisy, or as a complication, sometimes a sequel, of pneumonia, or from the rupture of a tuberculous or gangrenous area in the lung, or more rarely, a subdiaphragmatic abscess or a diseased viscus may perforate into the pleura. In children it occasionally seems to be primary. The exudate consists of thin or thick pus, and the action of the pus cells tends to digest the fibrin. If putrefactive organisms be present, the pus becomes very fetid. If the condition be not relieved surgically, the consequences may be very serious; the patient may die of exhaustion, of toxemia, or the pus may rupture into the lung with formation of pyopneumothorax, or through the chest wall (**empyema necessitatis**), or into neighboring organs. If unrelieved, it occasionally happens that the fluid is absorbed, the pus becoming inspissated, and later, infiltrated with calcareous salts, so as to form a solid plaque. Should the patient survive, there is usually great thickening of the pleura and even deformity of the chest. Practically it must be remembered, in view of the serious nature of the disease and the readiness with which it may escape recognition, that the physician will oftener regret his delay than his precipitancy in the use of the exploratory puncture needle in a doubtful case.

Hemorrhagic Pleurisy.—Bloody exudate is found in tuberculous pleurisy or where new growth is present in the cavity, although not

of necessity; further, it may occur in the very debilitated, or those suffering from scurvy, icterus, or the hemorrhagic diathesis.

Productive Pleurisy.—This may be a late development of a simple exudative pleurisy, or may arise insidiously as a primary affection. Slight degrees of thickening of the pleura are pathologically unimportant and clinically equally so. In the more marked cases the pleura is much thickened, even to a centimeter or more, becoming a white membrane, sometimes of a pearly or cartilaginous appearance, and in extreme cases, resembling the icing that is put upon a cake (**hyaloserositis**). On microscopic examination, this proves to be layered, and otherwise almost structureless, save that in its deepest parts there is slight vascularization; the lung is apt to participate in the state of induration, and often a neighboring serous surface is likewise involved, especially the peritoneum over the spleen and liver. With the lapse of time, calcareous masses or plates of cartilage and bone are formed.

Tuberculosis of the Pleura.—Not infrequently a patient previously healthy develops pleurisy with effusion; such a pleurisy, coming "out of a clear sky," is likely to be tuberculous, and even if no lesion of the lung or elsewhere be found, it is needful to consider that the patient is tuberculous until it is proved that he is not. The tuberculous infection in such a case has been picked up from the lymph nodes or from a focus in the lung too small to be discovered by physical examination.

The pleura may be affected as part of a general miliary infection or from a tuberculous bronchopneumonia; in the former case the tubercles alone may be seen, and inflammatory reaction in the ordinary sense of the term is very slight, while in the latter, after the fibrin has been removed, the tubercles show on the surface of the pleura, indicating the nature of the infection. When it is desired to test the fluid with a view to determine if it be tuberculous or not, the nature of the cells whether lymphocytes or leukocytes should be determined, and the sediment from the centrifugated fluid should be inoculated into a laboratory animal. It must be remembered that there are cases showing no obvious tubercles, appearing to be cases of simple serous pleurisy, in which inoculation of the fluid into animals sets up tuberculosis. In advanced cases, considerable caseation may be found, layer after layer of tubercles undergoing in succession the necrotic change.

Rarely, **syphilis**, **leprosy**, and certain **parasites**, such as echinococcus, psorosperms, and entamœba coli have been known to affect the pleura.

Progressive Tissue Changes.—**Tumors.**—Of benign growths, **fibroma**, **lipoma, chondroma, osteoma,** and **angioma** affect the pleura; of malignant growths, the most important is **endothelioma**, which is found in the pleura more often than anywhere else, save the dura. It may be soft and circumscribed, but more often is firm, flattened, and cancer-like. **Sarcoma** of the pleura is occasionally found in the young; various combination forms of sarcoma, such as angio-, fibro-, and chondrosarcoma are met.

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THE MEDIASTINUM

The mediastinum is that part of the thorax which lies between the two pleuræ, the sternum and the vertebral column. Since it is a space or a place in which there is only loose connective tissue containing many organs and different sorts of tissue, and not an organ or system of organs, its diseases cannot be taken up in any rational or sequent way; some generalities, however, are necessary. Leaving aside the vessels, nerves, muscles, the trachea, œsophagus, thymus, and the thoracic duct, we have still left for consideration the loose connective tissue that lies among these, and the very important groups of lymph nodes.

Fig. 291
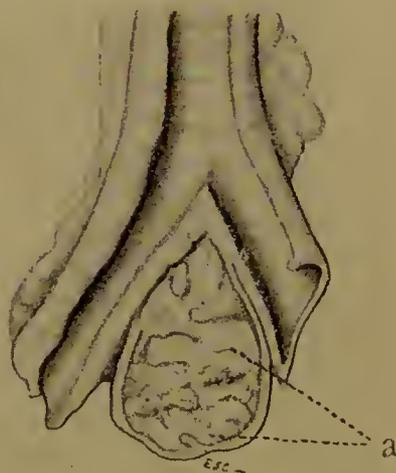
Tuberculosis of lymph nodes below bifurcation of trachea in a child: *a*, enlarged caseous node. .
(McGill Pathological Museum.)

Inflammation.—Mediastinitis.—Mediastinitis is inflammation of this connective tissue; it will be seen that such can arise in many different ways, by trauma or by extension from any of the numerous structures referred to as occupying or bounding the space, or finally, by the infective agent being carried thither in the blood. An inflammation may resolve or, on the contrary, may progress to the formation of an abscess, which may rupture to the outside or into one of the many organs of which it has choice. Should a considerable inflammation, which has not been suppurative, become healed, mediastinal adhesions arc apt to remain; these may link the pericardium to the chest wall, or the pericardium to the pleuræ, and may be so dense and numerous as to obliterate the space. Apart from such acute disease, the slow progressive inflammation spoken of as producing the thickening resembling a cake icing tends to affect the mediastinal tissues along with the pleura and the pericardium.

In the frequent references made to thoracic lymph nodes as the places in which tubercle bacilli and other infective agents lie latent or from which they set out to infect the body at large, the large groups

of nodes in the mediastinum are those referred to; not only those which are strung along the course of the vessels, the œsophagus, and the trachea, but the large groups at the bifurcation of the trachea, and around each bronchus. The size of these groups and the importance of the tracts they guard make them of great use in handling large amounts of infective material, from which they are necessarily liable to injury. It is in them that signs of latent and healed tuberculosis are oftenest found. Simple inflammation of these groups may lead to their great enlargement, and to consequent pressure upon the viscera in the space, or to their adhesion to the walls of viscera, such as the œsophagus, with subsequent deformity of the same by traction.

Progressive Tissue Changes.—Tumors.—Considering the tumors of the mediastinum, the multiplicity of tissues makes it possible to have many different forms of new growth; the only forms that require special mention are the **dermoid cysts**, which arise from the thymus gland or from epiblast shut in at the closure of the thoracic wall. These are soft, fluctuant, and are apt to transmit pulsation from the great vessels, so that they may be mistaken for aneurysm. There is danger that they may rupture into some important structure. **Teratomas** proper— fœtal inclusions—are rarely encountered. **Sarcoma** is the most common malignant tumor of the mediastinum, arising either from the connective tissue or from the lymph structures, from which **lymphosarcomas** of enormous size grow. Many of these mediastinal tumors, however, originate from the lymphoid tissue of the thymus, and of these some, at least, exhibit the characters of an inflammatory granulomatous growth—**lymphogranulomatosis.** Secondary malignant growths obtaining place in the lymph nodes or elsewhere are of fair frequency, and are clinically important, as are the primary growths, by reason of the importance of the structures upon which they may exert pressure. The vagus, the sympathetic nerves, the œsophagus, trachea, and the various vessels are so close together that a relatively small tumor may be attended by great disturbance of function.

THE THYMUS

The thymus is developed primarily from the hypoblast of the third branchial groove just as the tonsils are derived from the second, and, like the tonsils, while originally of epithelial type, their epithelium becomes surrounded and largely replaced by lymphoid tissue, the remnants forming concentric masses of cells known as Hassall's corpuscles. To all intents and purposes it is a lymphoid organ forming two elongated and fused lobes in the anterior mediastinum and extending over the upper portion of the pericardium. Reaching its maximum development at about the end of the second year of life it then undergoes a premature senile **atrophy** of a somewhat remarkable type. The lymph cells progressively diminish and their place is taken at first

by cells which contain small fatty globules and later by what appear to be true fat cells. Occasionally it persists until the fifteenth year or later and is of considerable size, with abundant lymphocytic elements. Diseased conditions of the thymus are rare; the most important is the thymus **hyperplasia** generally accompanying the **status lymphaticus (lymphatism)**; this hyperplasia occurs in young children, but has been noted in young adults, weights of 50 to 70 grams being recorded, the maximum of the normal gland being 37 grams. In leukemia there may be marked enlargement as also in some cases of exophthalmic goitre. Rare cases of **abscesses, tuberculosis,** and of **syphilitic necrosis** have been described.

Tumors are rare, with the exception of **lymphosarcoma.** As above noted, it appears probable that a large proportion of the diffuse, locally infiltrating growths of the mediastinum originate from the thymus gland.

CHAPTER IX

THE NERVOUS SYSTEM

GENERAL CONSIDERATIONS

When we recall the extraordinary complexity of the finer anatomy of the brain and cord, the relatively small area of the surface of the cerebral hemispheres in which we can recognize the existence of "centres" controlling one or other function of the body, the vast mass of cerebrum and cerebellum, regarding the function of which we have no sure indications, the remarkable system of multiple associations between the neurones, the great bulk of data and of hypotheses that has accumulated, we confess that it is with trepidation we enter upon the task of compressing into a few pages even the minimum of knowledge required by the beginner in medicine. As to the nature of thought and the association of ideas, the highest of all the cerebral activities, we know practically nothing; the same is true regarding the essential nature of memory; it is only when we come to the relationship between the higher centres and certain bodily functions that we find ourselves on somewhat surer ground and this because we can follow and recognize the tracks of anatomical change. But even here, although for long years investigators have been studying the nervous phenomena of such all-important matters as the periodic activities of the circulatory and respiratory

system, there continues to be uncertainty as to the exact nature of the automatic mechanisms that govern these, and as to the exact site of the controlling neurones.

The entire nervous system is made up of a great aggregation of similar units, the **neurones**; each neurone consists of a **nerve-cell body**, **dendrites** and **axone**. The gray matter of the brain and the ganglia possesses a preponderance of nerve-cell bodies while the white matter and the peripheral nerves are largely made up of axones. The neurones are held together (or held apart) by **glia** and **fibrous tissue**, the latter, in small quantity, serving to support the blood vessels of various sizes; definite lymph vessels have not yet been proved for the substance of the brain, although these exist around the blood channels. Each neurone is anatomically independent of all other neurones.

The nerve-cell body assumes varying shapes, has a usually central nucleus, with a definite nucleolus, and in its protoplasmic substance a meshwork of fine fibrils in the interstices of which lie variously shaped bodies of stainable substance (**chromophilic, tigroid, or Nissl's bodies**), which are presumed to be of nuclear origin, because their substance has stain affinities somewhat like those of the nucleus. The dendrites are tree-like prolongations of the protoplasmic substance of the nerve-cell body, tapering, becoming smaller as they recede from the cell, very numerous and branched, serving to bring the protoplasm of one nerve-cell body into "almost-contact" with other cells. The term "almost-contact" is used, because it is generally believed that actual contact does not occur, but that parts of two nerve-cell bodies thus lie in juxtaposition as do the secondary and the primary coils of an induction battery. The axone or axis-cylinder is a process of the cell, usually single, containing no chromophilic bodies (nor are there any to be seen in the part of the nerve-cell body from which it takes its immediate origin) and is of uniform size throughout; toward its end it may split it up into a terminal tree, of which each twig may end in an end-foot or end-plate which is in intimate relation (actual contact) with the cell (*e. g.*, muscle) to which it runs. The axone, as it leaves the nerve-cell body, becomes invested by a myelin sheath, and axones so sheathed make up the greater part of the bulk of the white matter of the brain and cord. A number of sheathed axones, surrounded by the sheath of Schwann, constitute a peripheral nerve; the sympathetic nerves possess a sheath of Schwann, but are not myelinated.

On the Correlation of Neurones.—It is only the very simplest reflex act, apparently, that depends upon what we may term a simple arc, and that simple arc calls into play two neurones. This may be laid down, that a given axone conveys stimuli in only one direction. Thus, a sensory or afferent stimulus has to be conveyed to the spinal cord through the agency of at least one neurone, and the muscular response to such stimulus has to be conveyed from the central nervous system by at least one other neurone. As already stated, each neurone is isolated to the extent that, although it may come into contact with

another neurone by means of its arborization, there is not an inter-cellular union. Communication between neurone and neurone is in the form of arborizations surrounding the nerve-cell body of the second neurone, and impulses passing down certain of these arborizations have to jump across the material, or **synapse**, intervening between them and the second neurone. For more complicated reflexes, and for voluntary acts, a stimulus may have to pass through several cell relays before the act in response to the primary stimulus can be instituted. In the complex, as in the simple arc, a break in any one relay prevents the response, or if it does not prevent it, causes definite delay in its production, because the stimulus has to pass along some more round-about path, which may not always be provided. If the break be on the afferent side, we have loss of sensation, if on the efferent side, loss of functional response.

Groups of Neurones.—We are accustomed to recognize three great groups of neurones—the afferent, the efferent, and the sympathetic.

The Afferent System.—The afferent nerves of the body in general are represented by neurones whose nerve-cell bodies are situated in the posterior root ganglia of the spinal cord, and in certain corresponding so-called centres in the bulb and pons, and even farther forward in the base of the brain. Cerebral sensory nerves, olfactory, optic, etc., are similar to the somatic sensory nerves in this, that all alike must transfer their stimuli to other neurones which conduct them, by more or less devious paths, to the cells of the cerebral cortex, and to other related cells of the higher order. The appreciation of sensation lies in these cells of the higher order, whereas the reflex act produced in the simple arc may be accomplished without reference to the brain, and therefore without appreciation on the part of the individual.

The Efferent System.—The efferent nerves of the body are represented by a lower group of neurones whose nerve-cell bodies are situated in the anterior horns of the cord and in corresponding centres in the base of the brain. These, however, are under control of a higher group of neurones, or more strictly of two groups of neurones, the one whose cell bodies are situated in the cerebral cortex, the other in the cere-bellum. We still are by no means informed as to the full functions of these two orders of neurones. The cerebellum is presumed to be constantly responsible for the preservation, by means of rhythmic stimuli, of the interaction of the muscles, that is, it exerts a **static** influence, continues, so to speak, the *status quo* of the body musculature; departures from this state, such as voluntary movements, are instituted by the cells of the cerebral cortex. This may be made clearer by saying that the *status quo* of the body, whatever its posture at the time, is preserved by the (unconscious) **tone** of muscles, to illustrate which it may be pointed out that man keeps a certain posture without apparent effort, but really by the contraction, properly coördinated, of many muscles; this state of the muscles is in response to constant stimuli from the cerebellar cells; if, now, one wishes to move voluntarily, the

cells of the cerebral cortex take command, and by stimuli reinforce the action of some, lessen the action of others, introduce, it may be, the action of yet other antagonistic muscles, and so alter the *status quo* to a new status of voluntary activity.

The Sympathetic or Autonomic System.—This system is a very complicated special section of the nervous system, regarding which it may be said, that the abundant investigations of the last few years by Langley and others, have introduced so many new points of view that it is extremely difficult in a few words to describe either its anatomy or its function. Briefly, in connection with the brain, the main spinal cord, and the sacral region, certain fine nerve fibrils pass out. These fibrils having their nerve-cell bodies within the central nervous system leave this in connection with motor, or what (in the brain) correspond to motor roots, and terminate in a series of fine arborizations around the nerve-cell bodies of certain ganglia, which, save for these fibres, are isolated from the main nervous system. Thus, for example, the third cranial nerve contains fine fibres which pass to the ciliary ganglia; the seventh and ninth fibres passing to the submaxillary and sublingual ganglia, and to the sphenopalatine and otic ganglia; the autonomic or sympathetic fibres of the tenth and eleventh nerves run in the vagus, and it seems probable that these fibres end in small ganglia situated in or near each of the organs supplied by the vagus. As regards the spinal cord, the sympathetic fibres pass out by the anterior motor roots to the series of vertebral ganglia, including the superior cervical ganglia; in the sacral region of the cord, slight differences of arrangement of the sympathetic system to the anogenital region are observed.

These fibres running to various ganglia are the **pre-ganglionic** fibres which arborize around the cells in the ganglia; these cells in turn give origin to axones (the **post-ganglionic** fibres) which course directly to the viscera, or in the case of cutaneous fibres, return to join the spinal nerves and so course to the various segments along with the cutaneous sensory nerves. In whatever ganglion this relay is situated, it appears that there is no further relay, but that the axone of the second cell passes direct to the viscus which receives the sympathetic innervation. For example, in the dorsal region we have both vertebral ganglia and the conjoint ganglia of the solar plexus; sympathetic fibres from the cord pass through both of these to their ultimate distribution; their relay cells may be in one or the other but not in both. As regards the afferent fibres of the sympathetic system, these when present run in the white rami; it seems that the head and the skin have few or no afferent sympathetic fibres, these coming essentially from the thoracic and abdominal viscera. So, further, it appears that the sensory connection of the various viscera with the spinal nerves differs but little in arrangement from their motor connection.

Pathological Changes in the Nerve-cell Body.—What knowledge we possess concerning the changes that occur in the finer structure of the nerve-cell body is largely due to the employment of Nissl's method

which uses a staining material compounded of methylene blue, thionin, toluidin blue, and neutral red. Small masses and granules in the protoplasm thus become visible, arranged in different ways according to the type of cell. It may be mentioned that experience and extreme caution in the observation and interpretation of results obtained by this method are necessary. In a general way we know from the appearance and arrangement of the stainable substance what is the physiological state of the cell; the stainable material (tigroid) is normally in granules, spindles, lozenges, rodlets, threads, or shapeless masses occupying the interstices between the fibrils; it is not demonstrable in the embryo, it increases in amount within limits in a state of rest, and diminishes by activity and fatigue, in intoxications, in circulatory and nutritive disturbances, diminishes in advanced age and undergoes a degeneration into a finely granular material. Electric stimuli, and the activity consequent upon them, lead to swelling of the cell body and nucleus and to diminution of the stainable substance; if carried to the extent of producing fatigue, cell body and nucleus diminish in size and stainable material in quantity, and vacuoles appear. By section, compression, electric or chemical stimulation of peripheral nerves, the changes brought about in the cell are divisible into two stages, those of reaction and repair. The stage of reaction is characterized by a diminution of the stainable material (chromolysis, tigrolysis); this appears to be diffused more generally than usual through the cell, whose protoplasm, as a whole, becomes more readily stainable. This dissolving action seems to begin at the centre, the cell swells, and the nucleus comes to lie nearer the periphery. These changes are produced but slowly, the reactionary state being visible a couple of days after section of the nerve, remaining evident for two or three weeks and passing gradually into that of repair, in which the nucleus becomes once more central and the swelling disappears.

Pathological Changes in the Dendrites.—We know but little of the finer changes that occur in the dendrites, although they have been studied in dements and after the action of certain poisons. In diseases caused so diversely as these, we are able to see lesions that are relatively similar; which means that the methods at our disposal are able to detect only the most gross kinds of lesion, while the finer differences entirely escape our notice. We can make out atrophy of the fibrils, swelling and twisting of the same, and localized swellings. In the case of large cells, such as the Purkinje cells of the cerebellum, there are buds or gemmules to be seen on the twigs of the dendrites. When damage has been wrought these buds may be seen to be swollen, and to be cast off or disappear. We suppose that such swelling of the nodules, and to a greater extent such casting-off, interferes with the conductivity of the cell, so that this state of the dendrites is accompanied by impairment of the mental, the sensory, and the motor functions.

Pathological Changes in the Axone.—The idea which is most widely entertained at the present day is that the nerve-cell body exerts a trophic

influence upon the entire axone; that the axone maintains its nutrition only when it remains connected with its nerve-cell body. Thus, if a motor axone be cut, that part of it which is separated from the cortical cell or the anterior horn cell degenerates and dies, and if a sensory axone be cut, the part separated from the spinal ganglion cell ultimately withers and disappears. Whatever the course of the axone, however intimate its relations with other axones, its life as an axone depends upon its nerve-cell body, and if it be separated therefrom it is useless, just as one of a hundred telegraph wires might be useless if cut off from its battery. The one wire looks like the other ninety-nine, but no messages are passing over it. As a result of severance from the nerve-cell body, the axone in a short time—twenty-four hours—shows a swelling of the myelin sheath; this presently becomes changed into a series of globules of various sizes, of a fatty nature, which ultimately disappear by a process of digestion and absorption by the cells of the sheath of Schwann. The axis cylinder proper becomes irregularly vacuolated, broken, and granular, and likewise ultimately disappears, its place being taken by proliferated sheath cells and fibrous tissue, a replacement designated by the general term sclerosis. Nor is degeneration necessarily confined to the distal part of the axone; it may happen that the parent cell degenerates, apparently from lack of occupation, since it no longer can transmit messages or stimuli—**disuse atrophy**—and such atrophy applies alike to all parts of the neurone. **Regeneration** of a severed axone takes place, within limits. Where a nerve has been torn apart, the injury of the tearing sometimes extends a short distance up the nerve trunk toward the nerve-cell body, and may be followed by degeneration, but with a clean cut the proximal end quickly shows regenerative changes in the form of fine ramifications terminating in delicate filaments, the axone itself separating into its constituent fibrils, some of which terminate in a little cone of growth. The central end of the axone by the forward movement of the fibril referred to can extend from the point of section and join itself to the distal end, provided there be not too great an intervening gap. The bridging of the gap between the severed ends is accomplished by the extension of the central axone, using the damaged nerve or some other tissue, or even a mechanical insertion as a scaffold, and seeking the course of the destroyed distal axone by chemiotropism or attraction toward the sheath cells of the degenerated fibrils of the distal part. It is evident that the old axis cylinder undergoes complete degeneration, and recovery of function is not complete until the new axis cylinder processes have travelled down the old sheaths, even until they reach the site of and form new end-plates in the muscle, or in the case of sensory nerves, new sensory filaments in the end organs.

Such gross damage as we have been considering is not the only cause of atrophy and degeneration of the axone, for there are at least two occasions upon which atrophy can occur without a definite interruption to the continuity of the peripheral nerve. Comparatively mild toxins

acting during a long time, especially if accompanied by functional activity, may damage the nerve-cell body to an extent, slight but sufficient to interfere with its nutrition as a whole. Under these circumstances, the most outlying part of the neurone—the terminal part of the axone —suffers most, and the nutrition which did not suffice for the whole neurone may suffice for the neurone minus the most peripheral part, which is thus sacrificed to the welfare of the whole neurone, much as a beleaguered and starved city might save itself by sacrificing its most outlying garrison. Where the peripheral part of the axone begins to atrophy in this way, we may predict that the entire neurone will ultimately share the same fate. A second kind of degeneration is that to which we have previously referred as **abiotrophy**, in which, by reason of some congenital lack of vitality, the stress of ordinary neurone work is too great, and the structure atrophies under a stimulus that would not damage a healthy neurone; such a neurone begins and spends its life with so little spare energy at its disposal, that the ordinary expenditure of energy is too great for it and it atrophies prematurely.

Lesions of the neurone may be accompanied by a great variety of symptoms, and these it is not possible to particularize, comprising, as they do, all kinds of definite and indefinite aberrations of function. Of the definite functions possessed by the neurone we are able to note that (1) the stimuli which excite muscular contraction may be absent or weak or, if present, inefficient, so that the muscle rests in a state of **partial** or **complete paralysis**; (2) or, contrariwise, the stimuli may be so frequent or so extreme as to excite a disordered and too great activity of the muscle. These changes in the state of the nerve may be correlated with an actual lesion which we can see; but it may not be so, and although the two states are widely different from one another, we may not be able to distinguish any difference in the neurone, nor may we be able to tell that it is actually the neurone that is at fault. If we see no pathological change in such a neurone, we say that the fault lies not in any organic alteration of the neurone but in its function, and we describe such alterations of the normal performance of the organs as **functional**. It is not possible to say that **functional diseases** (so-called) are attended by no organic change in the neurones; all we can say is, that if there be change, it is not to be detected by our present methods.

Similarly, in the sensory neurone whose impulses pass from the periphery of the body to the nervous system we find that certain lesions of the neurone destroy the conducting power completely; or, again, with no visible alteration, we discover that the function of the sensory neurone is altered or absent—that, like a badly manned telegraph line, there may be no messages at all (**anesthesia**), that the message initiated at the skin may be exaggerated (**hyperesthesia**), or may be entirely paraphrased from its true meaning (**paresthesia**). To make the matter more confusing, any of these deviations from the true function of the neurone may not be due to inefficiency of the neurone at all, but may

be mental, just as the messages taken by a bad receiver from a good telegraph line might seem to indicate that the line itself was inefficient. The sum of all this is that there is little known about the organic changes that happen in the neurone; that wherever we observe disordered function without a correlated lesion, we call the disorder *functional;* that many disorders, today called functional, may prove ultimately to be due to organic change; and that a knowledge of the highest function of the nerve-cell body, even thought itself, is, as yet, a closed book.

GENERAL DISTURBANCES OF THE NERVOUS SYSTEM

Before proceeding to the consideration of the organic changes found in the nervous system, it is necessary to discuss briefly some of the disturbances seen in it which are not referable to a definite cell, or a group of cells, or a special peripheral nerve, but seem to involve a large part of the entire system or at least a very important part of it; such are *delirium, convulsions,* and *coma.*

Delirium.—Delirium is an affection of the mental function, in which judgment and the appreciation of the relations of surroundings to one another or of the patient to surroundings is impaired. The special senses may or may not be dulled, but, at the best, understanding of the messages they convey is obscured, and misinterpreted. The degrees of mental confusion vary widely; delirium may be the dangerous fury of the maniac, the meaningless shouting of the terrified but half-unconscious drunkard, or it may be the disordered dreams of the quiet, febrile patient, whose mind wearies itself by hearing the fancied rattle of a machine or by the ceaseless repetition of some imaginary task or voluntary action. Active as the mind seems to be, and great as is the expenditure of energy, there is usually a corresponding dulling of consciousness in some other direction; there is at times physical activity so great as to require restraint, or the muscular activity may be reduced merely to picking at the bedclothes, **subsultus tendinum** (a voluntary act misdirected), or there may be visible only a tremor.

Delirium is often an accompaniment of the pyrexia of the various infective fevers, typhoid, typhus, smallpox, pneumonia, and rheumatism, but is rather a manifestation of the presence of a toxin than a mere accompaniment of hyperpyrexia. **Delirium tremens** is an example of the effect of an unaided chemical poison; the delirium of a child in pneumonia represents that arising wholly from an infective agent and its toxins; the delirium of acute mania is an instance of that form which arises in the brain without a known physical cause—and the diversity of these forms indicates how hopeless a task it would be to define the affection in any pathological sense.

Coma.—Coma is a state of **unconsciousness**, and represents not so much an actual derangement of the function of the lower nervous system as a state in which there is an arrest of the highest, the mental

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functions; the control which mentality exerts on the lower nervous system is lessened or absent. Thought, perception, volition, and voluntary movements are in abeyance; if the coma be not of the deepest, reflex movements can be instituted, but the muscles are relaxed; the centres, such as the respiratory and circulatory, which are automatic, are depressed in their activity, but their functions are by no means abolished. Concussion, pressure, exhaustion from previous excitation, and toxins appear to be effective causes of this state.

Convulsions.—A convulsion is a series of involuntary contractions of the muscles; if only a few muscles are concerned or only a single part of the body, the term **spasm** is usually applied, while the term convulsion is used to describe the phenomenon occurring in all or many parts of the body together. Consciousness may or may not be lost; the convulsion in any case is quite apart from the action of the will. Let the reader think for a moment of a motor nerve cell with its axone and the muscle supplied by it; voluntarily, he may send a stimulus to the muscle (and certain of its neighbors). The message calling for muscular movement goes down the wire, the axone, and as a result the muscle contracts. It is as if the muscle were a marionette that performs when the wire is pulled. In diseased conditions misdirected stimuli may come to the nerve cells from various sources and these stimuli may produce disordered purposeless muscular movements. To follow our simile, it is as if a mischievous boy found his way to the keyboard which controls the marionettes; instead of pressing them in their proper order so as to produce coördinated action of the marionettes, he does his best to make them all work at once, and the figures dance in a hopeless disorder. In the brain, it may be a toxin which irritates, or it may be a near-by tumor, or a clot of blood which presses the brain cells—in any case, like the boy with the wires of the marionettes, the irritant plays upon the nerve cells: they send out impulses and the muscles dance.

This leads us to say here a few words regarding the normal **tonus** or physiological state of the muscle and the significance of exaltation and depression of the same. All the cells in the body may be said to have an intrinsic **tone**, but in the voluntary muscles it is clear that we deal with more than this, for if the nerve going to a muscle be divided, the muscle immediately passes into a flaccid state; or otherwise, stimuli are constantly passing down the nerve from the central nervous system, which stimuli without any act of the consciousness or will, maintain the muscle fibres in a condition of relative partial contraction. The next question is, what is the nature of these stimuli? Is it a constant outflow or does the tonus of the muscle represent the summation of periodic and rapidly repeated impulses? The delicate string galvanometer applied to motor nerves informs us that the latter is the correct answer; that, in health, each voluntary muscle receives stimuli reaching it at the rate of from five to fifty per second. These stimuli are minimal but sufficient to set in action those associative and dissociative processes

which lead to contraction. When the neurone is fatigued, the rhythm seems to be slowed, and apparently the rate of rhythm in coördinated muscles is subject to variation, that is, may not be the same for the flexors and the extensors respectively; in this way we may explain the **tremors** of cases of nerve exhaustion as due to a lack of correspondence between the rates of contraction of the flexors and the extensors of a part. This **tonus** then is a "state of preparedness" of a muscle; the difference between tonus and voluntary contraction is a matter of degree—in a normal contraction there is not a single impulse but a like series of rhythmic, rapidly recurring stimuli, apparently at the same rate as, but individually stronger than those necessary to produce and preserve tonus.

In describing convulsive movements of the muscles, it is usual to distinguish **tonic** and **clonic** contractions; in the former the stimuli occur so rapidly that the proper time of relaxation is not granted to the muscle, and a continuance of the contracted state happens—tetanic or *tonic* contraction; in the latter either by partial tiring of the muscle or by a less rapid series of stimuli, the muscle goes alternately into the contracted and the relaxed state—*clonic* contractions. The term **clonus**, by usage, has come to have a slightly different significance. By clonus we mean the phenomenon associated with tendon or muscle reflexes, where in place of getting a single response to a tap or pull upon a tendon there is elicited a recurrent series of contractions, due to conditions causing exaggerated muscle tonus.

The part affected by a convulsion may enable the observer to define the site of the lesion, especially if it be situated upon the cerebral cortex; here the cells of only one group or a few groups of muscles may be affected, in which case the convulsion is called **focal** or **Jacksonian** (Hughlings Jackson having first described it). Even if the lesion be strictly localized, it sometimes seems as if the excitation of the cells immediately affected could spread to others, in ever-widening circles, new cells being involved successively, so that the convulsion extends in that half of the body first affected, in a definite order. Convulsions are classified according to their origin, rather according to their supposed origin, for most of such a classification is pure conjecture; the difficulty of determining the cause of convulsions is enhanced by the differences of irritability of the nerve cells, not only in different persons, but in the same person at different periods. Nevertheless it is customary to say that the causes of convulsions are (1) **mechanical**, as when a tumor or hemorrhage in the skull causes extra pressure upon the motor nerve cells, or (2) **toxic**, as in alcoholism, uremia or lead poisoning, (3) **reflex**, *e. g.*, some cases of epilepsy, as when an inflammation or irritation in some distant part of the body (perhaps even pinworms) appears to be the cause, or (4) **functional**, when the stimulus appears to originate in the highest cerebral cells, that is, the cells concerned with thought and association. Stimuli of this sort are called **ideogenous**.

Focal or Local Changes and Their Results.—Distinct from the states just discussed, which concern the most important parts of the nervous system and through them affect the entire system, are those changes which remain limited to a part of the system, which are thus called **focal** or **local**. Where changes are evidenced by symptoms which point to the destruction or damaging of a neurone or a set of neurones, whether the damage be wrought in the nerve-cell body, the dendrites, or the axone, whether the neurone be motor, sensory, or sympathetic, any sufficient lesion in any part of it will be shown by a failure in its function—thus a muscle is paralyzed or is weak, sensations are not carried, or are carried incorrectly (paresthesia). The symptoms produced are thus dependent upon the nerve centre or the nerve path that is concerned, although it is of course to be remembered that the nervous mechanism may be intact and fully operative and a paralysis, for example, be due to some fault of the muscle or other structure concerned in the performance of motion.

Focal Symptoms in the Field of Motor Nerves.—From the moment at which the student begins to study focal symptoms, he requires an accurate knowledge of the situation of the various groups of nerve-cell bodies in the brain and cord and, of course, of the axones from these groups. Between the cortical cell and the muscle two neurones run— the upper and the lower motor neurone. The upper motor neurone has its cell body in the cortex, and its medullated axone crosses to the opposite side and there runs with other motor nerves, especially in the crossed pyramidal tract, to reach the nerve-cell body of the lower motor neurone, which is situated in the anterior horns of the cord. From the cell body in the horn the axone of this second cell runs by a peripheral nerve to the muscle. If the peripheral nerve be cut near the muscle all this elaborate mechanism is rendered temporarily useless so far as the muscle is concerned, and the muscle is paralyzed; if the upper motor neurone just below the cortical nerve-cell body be cut, the muscle is similarly paralyzed; how can one tell in which of these situations is the actual lesion? The nutrition of the muscle depends ultimately upon its connection with the nerve-cell body of the lower motor neurone; if the lower motor neurone be intact, nutrition is not interfered with, and the muscle responds to every stimulus which the nerve-cell body of the lower motor neurone chooses to send; and if the lesion be in the upper motor neurone, the cortical cell body has no governance over the lower cell body and the latter "breaks loose" sending frequent, uncalled-for stimuli to the muscle, which is thrown into a state of excitability (**hypertonus**) and, it may be, **spasm**. On the contrary, if the lesion be in the lower motor neurone, no impulses at all reach the muscle, which lies inert, flaccid, hypotonic, and, cut off from its nerve-cell body, quickly degenerates and atrophies. To recapitulate, *destruction of the upper motor neurone allows hypertonus or spasm in the muscle, destruction of the lower motor neurone, flaccidity and atrophy.* But this alone will not tell us which part of the tract is

destroyed; to determine this requires consideration of all the facts in the case. Much can be learned from the extent of the damage; if we consider the upper motor neurone, it will be apparent that a lesion, such as hemorrhage, though of small size, might affect a great many neurones, even those of half the entire body, if it attacked them where they are all packed closely together, as in the internal capsule. A lesion of the same size at the cortex could affect only the cells concerned with a part of a limb. Similarly, in the lower motor neurone, a destructive lesion in the middle part of the spinal cord might destroy the pyramidal tract and put out of service most of the muscles of a lower limb, whereas a lesion of the same size lower down might destroy only a few anterior-horn cells, and put out of service only a small group of muscles.

Depressive versus Irritative Disturbances.—We see, thus, that a muscle may be paretic or paralyzed by reason of some disease in the muscle itself, or, more commonly, by reason of some disturbance in the neurone which governs it; there is yet another way in which the same result is produced, and that is in the so-called **hysterical paralysis**; here the muscle is healthy, the neurone intact, but the muscle is not stimulated by its neurone, whose action is inhibited by the *mind* or, in other words, by some group or groups of cells which are concerned with the mental functions, and are the multiple governing power in the brain.

Hitherto we have spoken of lesions of the neurones, evidenced by paralysis or paresis of the muscles, that are due to prevention or depression of the function of the neurone—the so-called **depressive manifestations,** but there is another form of lesion, the **irritative.** Before pointing out what these are, it may be said that a lesion can destroy some part of the neurone, so that stimuli from that neurone cease entirely; or the lesion may merely interfere with the stimulus, which reaches the muscle in a weakened degree; or the pressure of the lesion may act as an irritant to the neurone so that it is stimulated. Being stimulated in a wrong way and from a wrong source, the messages it sends to the muscle are certain to be ill-timed and purposeless, because they are not instituted by the mind, as part of the properly coördinated plan of stimuli in obedience to which the proper muscular work of the body is carried on. These irritative lesions are important, and will be particularized; the signs by which they are accompanied are *tremors, choreiform movements, convulsions,* and the muscular activities that result in *contractures.*

Tremor.—Tremor is a series of consecutive "small" muscular movements, and is familiar to everyone as seen in some of the very old. The tremulous movement in different people may vary greatly in its rapidity and in its situation, being general or limited to one or several groups of muscles. Tremor usually ceases during sleep; sometimes it is lessened or prevented temporarily by the exercise of the will; in other cases it is seen only when some voluntary movement of the part is

made (**intention tremor**), in yet others, during rest. A form of movement closely related to tremor is **fibrillary twitching** of the muscle, in which the individual muscle bundles arc seen through the skin to contract quickly and rhythmically. Tremors are readily observed in some alcoholics, in paralysis agitans, in multiple sclerosis, in lead poisoning and many other states. We have already referred to the mode of production of muscular tone (p. 573). If the rate of these tonic impulses to two sets of antagonistic muscles be different it will be seen that there will be a lack of synchronism between the respective contractions of the two sets, so that the limb or part affected is drawn momentarily now in one, now in the other direction.

Choreiform Movements.—Choreiform movements are of the nature of intermittent clonic spasms; they appear as irregular, purposeless, jerky motions of the limbs, face, or body, and are seen in chorea, Huntingdon's chorea, spasmodic wry-neck, tic, and hysteria.

Convulsions.—Convulsions have been already considered (see p. 573).

Contracture.—These are the states of body in which the mobility of the limbs is lessened, and the position assumed by a limb is gradually fixed, so that it cannot be moved from that position. This occurs in two ways—a limb, for example, may be flexed by the activity of flexor muscles which are continually in a state of spasm, or by the action of normal flexors, *unopposed* by extensors, because the latter are paralyzed, while the former still receive the normal tonic impulses. This latter form of contracture is termed passive.

THE BRAIN

Gross Anomalies.—These may be divided in the first place into (*A*) those associated with malformation of the vault of the skull, which we may call cranial anomalies, and in the second place, (*B*) those of the brain alone, the cranial vault being intact.

(*A*) Of the former we have a remarkable series, associated evidently with imperfect closure of the dorsal groove in the region of the cephalic lobes, illustrating all stages in which this is either partial or complete or accompanied by a greater or less extent of imperfect closure of the somatic dorsal groove (**spina bifida**). **Anencephaly** or **acrania** is that form in which there is complete defect of the vault of the skull and of the scalp, and the brain is represented by a mass of congested membranes. The basal part of the brain is present and gives origin to the eye, the ear, and the cranial nerves. In **exencephaly** the defective development is partial; the vault of the skull is in part developed, most frequently the frontal region; there is imperfectly formed brain substance which overhangs, like a sack, the back of the neck, or in other cases, the eyes. As a result of amniotic adhesions, the projecting part may be lateral and unsymmetrical.

(*B*) Of malformation of the brain alone, the following are the most remarkable:

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(a) **General.**—Microcephaly, in the typical form of which the whole of the brain is small and poorly developed, the cranium, while perfect, being correspondingly small. The brain, instead of weighing 1200 grams, may weigh 250 grams or less. This condition is associated with idiocy, and is sometimes familial.

Macrocephaly is a condition of absolute increase in brain substance, rare, but well authenticated. Some, but not all of the greatest men in history have had large brains, notably Cromwell and Bismarck (over 2000 grams). The largest known brain (2850 grams) was, however, that of an idiot.

(b) **Local.**—There may be partial microcephaly, the cerebellum being well developed and the hemispheres of small size and with poor convolutions or *vice versa*. The cerebellum may be absent. More frequent is defective development of portions of one or both hemispheres; of this the most characteristic form is brought about by imperfect development or by intra-uterine obstruction of one or more branches of the middle cerebral artery. As a result there is either in the early stages a lack of development or in later foetal or early postnatal life absorption of the area supplied by that vessel, with, in consequence, the formation of a cyst-like space covered by the membranes, containing cerebrospinal fluid (**porencephaly**). More rarely, definite portions of the brain, such as the corpus callosum, may be undeveloped and wanting. A slighter defect is **heterotopia**, in which portions of the gray matter are aberrant and are found in the white matter.

There is considerable variation to be found in the development and number of the convolutions; in so-called degenerates, these may be reduced in number and shallow, from flattening of the gyri (**agyria**). In those of high mental development they are found well developed and abundant.

Circulatory Disturbances.—**Anemia.**—The brain is found strikingly bloodless, and of almost milky white color in cases of death from hemorrhage, as again in cases of profound systemic anemias.

Hyperemia.—Hyperemia of the **passive** order is seen in cases of chronic general congestion, as in cardiac disease, of obstruction to the venous outflow by way of the jugular veins, as in hanging, and in cases of suffocation or death in convulsions. The brain oozes more blood than usual on section and the cut vessels are more than usually prominent. **Active hyperemia** is seen in cerebritis, and in such states as mania, delirium tremens, and to some extent in cases of death at the height of acute infections. As in congestion, so also in œdema, the condition is best recognized by the state of membranes; cerebral œdema is recognizable by the pale, wet, and shiny surface on section. Œdema may be extreme in the vicinity of a new growth, the infiltrated brain tissue appearing actually gelatinous. The causes of œdema in general are those of extreme passive congestion.

Hydrocephalus.—Hydrocephalus is of two orders—external, where the excess of fluid is outside the brain (see meninges), and internal,

where the accumulation is in the ventricles. The latter is the more striking, and may be acquired during intra-uterine or postnatal existence. The condition is progressive and the head may attain an extraordinary size, the cranial bones becoming as thin as paper, or even replaced by membrane and widely separated. Through the unusual distension of the ventricles the brain substance becomes thinned to an almost incredible degree. There is still debate as to the cause, but even if in the first stages there is extensive formation of cerebrospinal fluid from ependymal irritation, etc., the main disturbance in a fully developed case is obstruction to the outflow of the fluid from the ventricles into the system of meningeal spaces, and so into the lymphatics.

Hydrocephalus of the fourth ventricle is rarer, but occurs as a result of obstruction in the lateral recesses in which run the choroid plexuses and which communicate with the subarachnoid space.

Hemorrhage.—Hemorrhages of the small vessels of the brain may occur in large number and of small size, from trauma, especially in concussive injuries and at the site affected by "contrecoup." They are seen near the surface on section of the brain substance. Large hemorrhages in these regions are rare, apart from actual laceration. Large hemorrhages, however, may occur, notably deep in the substance of the hemisphere, involving the internal capsule, corpus striatum, and optic thalamus, less rarely in the pons and base of the brain. These are often of large size, as much as several ounces of blood being effused, with great accompanying destruction of the brain tissue; the blood may escape into the ventricles. Why this should be the seat of election for cerebral hemorrhage appears to be due to the fact that the lenticulo-striate branches of the middle cerebral are almost in a direct line with the internal carotid and thus are subjected to the greatest force of the blood stream. From their position such hemorrhages are likely to involve the anterior two-thirds of the posterior limb of the internal capsule in which pass the fibres from the motor area of the cortex; the result is "apoplexy" or paralytic "stroke," both terms implying suddenness. A small hemorrhage may be completely absorbed; a larger may be absorbed with a resulting cicatrix; there is, however, little tendency to the formation of granulation tissue, and thus, if not fatal, a large hemorrhage is transformed into a **cyst** (see p. 413).

Embolism and Thrombosis.—Sudden apoplectic attacks may be due to causes other than hemorrhage. Of these the most important is embolism. The arteries of the basal region of the brain are end-arteries (see p. 424), wherefore it follows that if one of these becomes suddenly plugged by any foreign substance circulating in the blood, the area is cut off from its nutrition, and, as a result, the nerve cells in, and the nerve fibres passing through that area undergo disorganization. Cerebral embolism may be brought about, like embolism elsewhere, by many agents (see p. 434), but of these by far the commonest is the thrombotic material constituting the vegetations of acute endocarditis, which, broken off, may be carried into the carotids and so to

the brain, and the same reason that led to hemorrhage being specially frequent in the branches of the middle cerebral—namely the direct course of the blood—applies also to embolism; it is the arteries of the base of the brain that are specially apt to be involved. The result of such embolism is **encephalomalacia** or "brain softening," affecting the area of distribution of the artery involved. There is first developed an area of necrosis, which soon undergoes softening and is of yellowish, gelatinous appearance; most often there is no infiltration of blood from the surrounding veins (**white softening**), but occasionally this supervenes (**red softening**), giving place to brown or yellow softening as the blood pigment diffuses out and is absorbed. The difference between the results of embolism and of hemorrhage is that the former remains relatively circumscribed to the area of blood supply, whereas with progressive outpouring of blood the hemorrhage involves a greater area than is supplied by the ruptured vessel. Symptomatically, therefore, the paralysis following upon a hemorrhage is apt to be progressive during the time following its actual beginning.

Thrombosis is secondary to disease of the arterial wall or to an embolus. In order of frequency the causes of cerebral thrombosis are arteriosclerosis, syphilis, and acute infections (including those cases which follow embolism). It will be recalled that in the subjects of arterial disease the smaller cerebral arteries are peculiarly apt to show degeneration in the form of atheromatous plaques and of multiple miliary aneurysms. Such thrombosis, originating at one spot in the diseased vessel wall, does not suddenly, but gradually, lead to obliteration and closure; there is, therefore, in general, an absence of the true apoplectic or stroke-like onset. The results to the cerebral tissue may be identical with those just described.

Aneurysms.—Aneurysms of the extracerebral and basal vessels of the brain are not uncommon; they are saccular and of the size of a pea or bean, and may be the site of rupture. Of more importance are the multiple **miliary** aneurysms of the intracerebral vessels in advanced arteriosclerotic conditions; maceration of the brain reveals that these may be present literally by the hundred, just visible to the naked eye. It is the sudden giving way of one of the larger of these that is held to be the most frequent cause of cerebral hemorrhage.

Inflammation.—Acute Encephalitis.—This is not a very frequent condition, save as caused by trauma, and as it occurs in the superficial parts, associated with meningitis, and locally, as an extension from disease of the middle ear and cranial bones. Nevertheless certain of the acute infections are associated with diffuse and generalized disturbance of the brain tissue. In rabies, in acute polioencephalitis, to a less marked extent in influenza, in bacteriemia due to staphylococci, etc., in typhoid, and other acute infections, the toxic hyperemia is probably the cause of those symptoms which are clinically grouped under the term "**meningismus.**" Save the hyperemia, the changes are microscopic, and consist of perivascular exudate with infiltration of lymphocytes and leuko-

cytes. The nerve-cell bodies exhibit alteration of the Nissl's granules. In very acute cases, punctate hemorrhages may be seen (**hemorrhagic encephalitis**).

Abscess of the Brain (Purulent Encephalitis).—This may be of various kinds, **cryptogenic, traumatic, metastatic,** and **by extension** from nearby structures, especially the mastoid region of the skull. Occasionally a well-defined abscess is found in the cerebrum or cerebellum unassociated with any recognizable focus of infection elsewhere; doubtless in such the infection is hematogenous. Traumatic abscess develops usually by the immediate carriage of pyogenic organisms into the brain substance from the exterior, although it may happen that an injured area may be infected long after the infliction of the injury. Metastatic abscess is seen where there is suppuration elsewhere, this being a hematogenous (or lymphogenous) infection. Abscess arising by extension is most commonly seen in the temporosphenoidal lobe or in the cerebellum, secondary to suppurative mastoiditis; it may also occur by extension from the upper nasal region and from any of the bone sinuses, or from the orbit. Frequently the abscess in these cases is a direct continuation of the adjacent suppurative area, but it also frequently happens that it is separated from this area by a zone of intact, though inflamed brain substance; to explain this it is necessary to consider the possibility of a metastatic lymphogenous infection.

Brain abscesses may be minute or multiple, as in metastatic cases, but more frequent is the large solitary abscess, surrounded by a hyperemic, œdematous area, forming a rounded mass; the pus is characteristically greenish and thin; when at all old, there is present a well-formed lining membrane, with little or no tendency to subsequent fibrous repair; according to its position it may rupture externally, causing a purulent meningitis, or internally into the ventricles. Deep in the "blind" area of the brain, such an abscess may remain for years without obvious disturbance of cerebral function.

Syphilis.—Favorite site for spirochetes as is the brain, it is to be remembered that the most striking signs and symptoms of "cerebral syphilis" are meningeal rather than cerebral; the meningeal effects will be dealt with later. More than this, cerebral infection is very commonly secondary to meningeal infection. The following are the most common changes induced in the brain substance: (1) **encephalitis neonatorum,** which is found in newborn, often in stillborn syphilitics; its striking feature is a small-celled perivascular infiltration, together with an excess of granule cells (**Gluge's corpuscles**), scattered through the brain.

Throughout the syphilitic process there is a peculiar liability that there should be involvement of the cerebral arteries and arterioles, especially those on the surface passing in from the meninges. This shows itself in the form of (2) a diffuse periarteritis with small-celled and plasma-celled infiltration, mesarteritis, with small-celled infiltration and replacement of the middle coat, and intimitis with proliferation

of the endothelium, leading to a form of endarteritis obliterans. It is this process which seems to be the eventual cause of those degenerative changes which appear in such diseases as general paralysis of the insane (**dementia paralytica**).

(3) In addition to these diffuse vascular disturbances, we encounter the development of localized solitary or multiple **syphilomas (gumma)**. These syphilitic granulomas may attain relatively large size, 2 cm. or more across, with destruction and replacement of the brain substance, and irritation of the surrounding neurones—in short, may present those symptoms which characterize intracranial growths. The base of the brain is the most frequent site, and the cerebellum is rarely involved. In the early stages they are soft and jelly-like, with a whitish centre, but they become firmer and may even undergo caseation. As a whole, they are less sharply defined than tuberculous masses.

Tuberculosis.—Just as with syphilis, so with tuberculosis, there is a predisposition for the lesions to occur most extensively in connection with the meninges (see p. 598). In the brain substance, tuberculosis appears in the form of conglomerate tubercles of hematogenous origin; these are found especially in the young in the basal portion of the brain, in the pons, the temporosphenoidal lobes, and particularly in the cerebellum. In the earlier stage of growth the caseous centre is surrounded by a ring of small tubercles and small-celled infiltration passing imperceptibly into the surrounding tissue and invading it. By the progressive caseation of the centre, and extension of the periphery, large caseous tubercles are formed, as large as or larger than a hen's egg. The process may become arrested, in which case the surrounding fibrosis is firm and well defined, and the mass may be shelled out. Occasionally, the caseous material undergoes softening, in which case the appearance is much that of a "cold" abscess. It will be understood that in such a case we have a replacement (and more) of brain substance by new tissue and the consequent increase of intracranial tension which is so predominant a feature in cerebral tumor.

Other granulomas such as **actinomycosis, glanders**, and **leprosy** are uncommon.

Regressive Changes.—These may be diffuse and generalized, or local, involving sharply defined areas of the brain and their associated tracts of fibres.

General Atrophy.—General atrophy is best marked in the progressive diminution in size of the brain in the old. Here the brain in general shrinks, and the space so made is taken, both outside and inside the brain, by cerebrospinal fluid; the perivascular lymph spaces in the base of the brain are greatly widened so that cystic spaces appear in the brain substance, and the membranes, especially the pia, indicate their share in this change by appearing œdematous. The nerve cells of the gray matter undergo a marked diminution, individual cells shrinking, and losing their dendrites, becoming more oval, and finally disappearing, and this not in special areas, but here and there, apparently at random.

With this diminution of the nerve cells, there is both an apparent and also, it would seem, an actual increase in the more lowly glial tissue and fibrils, so that there results an apparent diffuse sclerosis of the diminished organ. Associated with this, the convolutions appear small and the gyri between them much widened.

Very similar appearances are met prematurely in cases of chronic lead poisoning and in some alcoholics. In both of these classes, the glial and fibrous overgrowth appears to be even more pronounced than in the senile brain. To another markedly atrophic condition we have already referred—that seen in **dementia paralytica**. Here it is that arterial changes of syphilitic origin, affecting the arterioles, characterized more particularly by a perivascular plasma-celled infiltration, are obviously the primary cause of the degeneration. With the consequent malnutrition, there is even more extreme degeneration of the cortical nerve-cell bodies (and of the neurones in their whole length) than occurs in senile atrophy. Over 95 per cent. of cases of dementia paralytica give a positive Wassermann reaction. This disease, therefore, must be regarded as an atrophy of the brain secondary to chronic syphilitic arteritis.

Local Atrophy.—This may be brought about by many causes, chief among which are circulatory disturbances, pressure of tumors or of overgrowth of the inner table of the skull, pressure of localized inflammatory processes and the disturbed nutrition set up by the same. In addition we must recognize abiotrophic phenomena due to inherited or acquired premature exhaustion of the neurones of particular areas of the brain, as also the disuse atrophy which may follow the cutting-off of neurones from their distal portions, either peripheral end-organs or arborizations around the cell bodies of other neurones. It is these partial atrophies that are so characteristically accompanied by degeneration of particular tracts, whether ascending or descending, and it is these that have given us the knowledge we possess of the finer anatomy of the brain and cord. The processes that occur in this partial atrophy are of the same order as those seen in the general atrophy just described.

Progressive Changes.—The structure of the brain differs from all other organs of the body in that both its specific elements, the neurones, and its specific connective tissue, the neuroglia, are of epiblastic origin. The mesoblastic elements in it are comparatively slight, consisting merely of the vessels and the small amount of connective tissue constituting their adventitia. It follows thus that progressive changes are mainly in connection with the epiblastic elements. Progressive changes in connection with the vessels are comparatively rare; these we may first discuss, in stating that **angiomas** have been recorded in association with the cortex, and then of pial rather than of cerebral origin. **Fibromas** and **myxomas** have also been recorded, the former larger, the latter small and rounded. So, again, there are very rare cases of cerebral **osteoma**. More frequently are encountered metaplastic osseous plaques of the brain membranes; these cannot be regarded as true tumors. Sarcomas originating within the brain substance are

distinctly rare if we except the most anaplastic form of glioma, the gliosarcoma. Nevertheless, occasional spindle-celled sarcomas are on record which can be only of connective-tissue origin. We shall refer to the **endotheliomas** when discussing the tumors of the brain membranes.

Glioma.—Here we must in the first place distinguish between this and a condition of **gliosis** or **gliomatosis**, in which we encounter one or more poorly defined areas of diffuse but pronounced overgrowth of the neuroglial elements. In such a case the tumor passes imperceptibly into the surrounding tissue, and, what is more, if it affect a convoluted area, the convolutions are still maintained, although they are markedly enlarged. This, it is true, is something beyond a mere hyperplasia, because in such areas the neurones have been replaced. What may be termed **true glioma** is usually solitary, tends to be spherical, and by its color and consistence is recognizably distinct from the surrounding tissue. In color the glioma is grayish pink, somewhat more translucent than the brain substance, and may be either relatively poor in cells but rich in fibrillar tissue (**hard glioma**), or may be rich in cells (**soft glioma**).

The glioma cell is characterized by showing numerous "spider-leg" processes, herein differing from the normal glial cell in which these processes are little noticeable, although there are abundant fibrils in the immediate neighborhood of the cells. Where the cells compose the whole of the tumor with their processes little recognizable, it is difficult and at times impossible to distinguish the tumor from a round-celled sarcoma of mesoblastic origin. Believing, as we have pointed out (p. 344), that the term sarcoma can be given only a histological significance, we do not hesitate to speak of such tumors as **gliosarcomas**, although many German authorities still maintain, from arguments with which we cannot agree, that this terminology is incorrect. Solitary gliomas are to be met with in the cerebral hemispheres as also in the cerebellum. There are not a few cases on record of glioma of the *corpus callosum* but this, in our opinion, is more accurately a diffuse gliomatosis. Occasionally we meet with gliomas containing rosette-like cell masses and actual cystic cavities lined by a cubical epithelium; such tumors are evidently of embryonal origin and represent aberrant portions of the ependyma that have been snared off in the course of development. We have already referred to the **ependymomas** (p. 365), tumors containing ependymal elements; these may be found forming nodular gliomatous masses in the lateral ventricles; a few cases from the fourth ventricle have been reported. Apparently these ependymomas may, though rarely, take on an epitheliomatous or carcinomatous appearance.

Secondary tumors in the brain substance are not so common as primary; not only are **carcinomas** and **sarcomas** met, but tumors, such as **hypernephroma** and **chorioepithelioma** are occasionally found, the two latter having more predilection for this site than the two former.

Cysts.—Cysts of various orders may be encountered in the brain; "gland cysts" or **ependymal cysts** arise by cutting off of part of the lateral ventricle; **hemorrhagic cysts** are secondary to large hemorrhages; **necrotic cysts** replace areas of softening, appearing also in connection with gliomas; here also may be included **porencephaly** (p. 578), and lastly **parasitic cysts** are found, the cystic stages of **cysticercus** and **echinococcus.** The former are small, multiple, attaining the size of a pea, rarely larger; the solitary echinococcus hydatids are large, even to the size of an orange, and from their size give all the symptoms of a brain tumor.

THE PITUITARY BODY (HYPOPHYSIS CEREBRI)

The pituitary body deserves separate mention, in that, while attached to the brain, its main constituent is not nervous tissue; it is, indeed, composed of three portions: the anterior glandular, an intermediate area with gland cells intermixed with neuroglial tissue, and the posterior junctional portion, also of glial tissue without nerve fibres proper. Little is known regarding its function save that the posterior and intermediate portions afford an extract which, like adrenin, greatly raises the blood pressure, and unlike adrenin, induces polyuria by acting directly on the kidney. The main pathological interest of the pituitary lies in the relationship between hyperplasia and adenomatous growths of the anterior portion and the development of acromegaly (see p. 96). Changes have also been seen in the pituitary in connection with pregnancy and castration, as again, secondary to removal of the thyroid gland.

THE PINEAL GLAND (EPIPHYSIS CEREBRI)

Anatomically the pineal gland represents a rudiment of the median eye still recognizable in certain lizards; it consists thus of purely nervous elements; at most, it may be the seat of hypertrophy and gliomatous tumors, which by their size may press upon the aqueduct of Sylvius and the vena magna Galeni and so bring about hydrocephalus internus.

THE SPINAL CORD

Anomalies.—Here may be recalled some of the more important congenital abnormalities of the spinal cord; they are relatively infrequent and do not call for extensive description. Incomplete formation and shortening of the cord is observed in cases of **anencephaly** combined with spina bifida as also in simple spina bifida, to which reference will be made later. Duplication of the cord has been observed both in cases of partial double monsters and apart from any clear evidence of

duplication of the body in general. Duplication of the spinal canal is also recorded; this may be partial or complete, when it appears to be the very slightest case of somatic duplication. More important, because more common and more obvious, are the various grades of **spina bifida (rachischisis)**. Here, anatomically, we deal with the various conditions of incomplete formation of the laminæ of the vertebræ, but underlying this, in the extreme cases is a lack of closure of the dorsal groove, whereby the two halves of the posterior portions of the cord fail to unite and the ependyma of what ought to be the spinal canal unites with the true skin.

Fig. 292
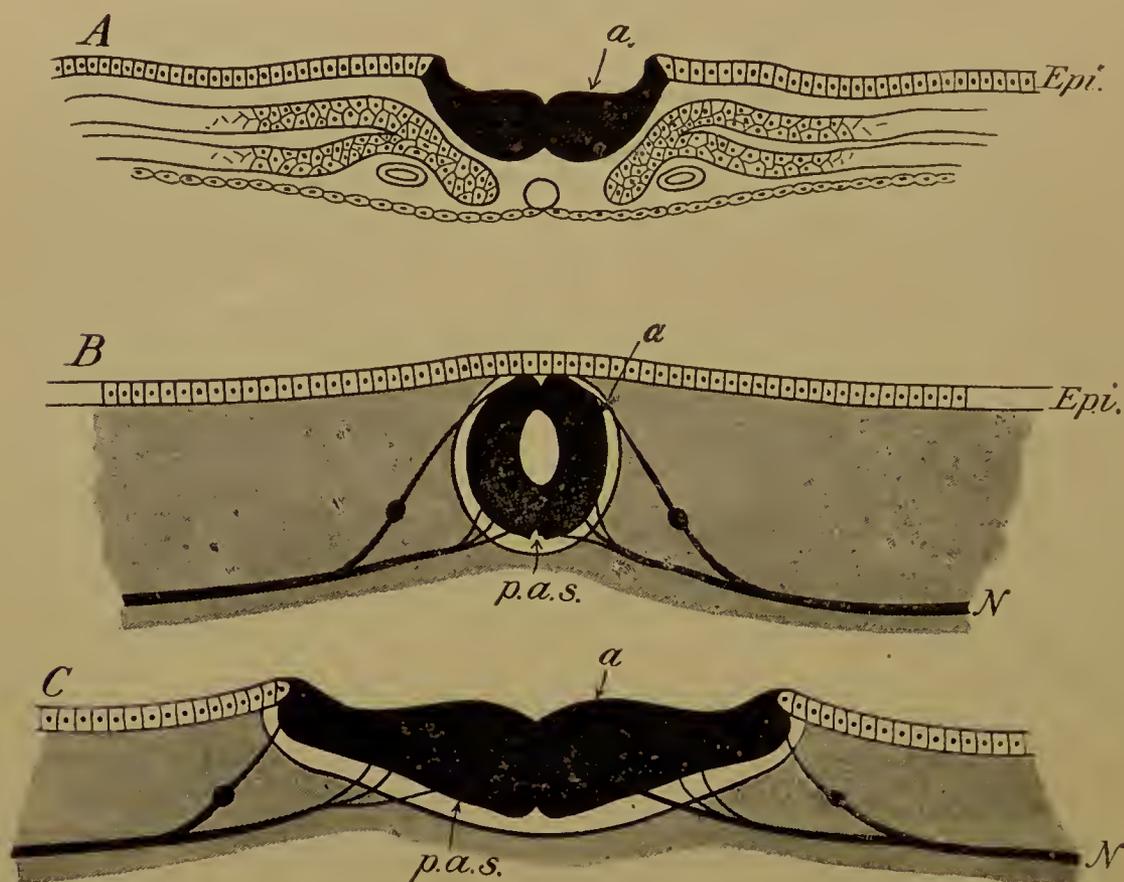
A, schema of development of medullary groove; B, formation of neural canal by closure of the medullary groove; C, complete rachischisis; the medullary groove remains open; Epi., epiderm; a, neural tract; p.a.s., pia-arachnoid space.

We shall later refer to the various forms of this condition in discussing the abnormalities (see p. 824). Here we repeat that the condition may affect the whole length of the cord, or may be partial, affecting a portion thereof, and may be complete or incomplete. Thus, under the cystic form of spina bifida, we may have a series of cases in which merely the laminæ are defective, the cord being perfect, the slightest form being the **spina bifida occulta** in which fatty tissue, in part developed in association with the spinal meninges, in part filling the defect of the bony and subcutaneous tissues, forms a projecting mass, which, curiously, is covered by a skin that is extraordinarily hairy.

This form is most frequently seen in the lumbosacral region and appears to be closely related to those cases of fatty projections covered by hairy skin which constitute "false tails." From these slightest cases we pass through a series of conditions of **meningocele**, in which the defect in the bony vault is occupied by a somewhat cystic expansion of the meninges filled with fluid, and in which the spinal cord is not involved, and to cases of **myelocystocele** in which, while the spinal canal is complete, the lack of support in the region where the laminæ are defective, results in a localized expansion of the spinal canal, to cases in which the spinal canal has failed to form and while the anterior dura and pia are fully developed, the spinal cord is represented by an imperfect and intensely congested layer of nerve tissue covered posteriorly and superficially by a layer of ependyma. In these cases occasionally owing to the want of support, fluid may accumulate in the anterior part of the pia-arachnoid space, forming thus a tumor projecting backward, the **myelomeningocele**.

Occasionally, wholly unassociated with any defect of the laminæ, there may be localized myeloceles or dilatations of the neural canal filled with cerebrospinal fluid (**hydromyelia**). This condition may be compared with **hydrocephalus internus**. As to the causes of the condition we know little, save that in some cases it appears to be congenital, in others acquired. Of greater clinical interest is the somewhat rare condition of **syringomyelia**, in which along the course of the cord is to be found one or more irregular dilatations of the central canal, which, so small in the normal cord as to be practically invisible, may be so distended as to admit a finger. In general these cavities are irregular in shape; in general, also, they are surrounded by a layer of hyperplastic glial tissue. The dilatation and cavity, being centrally located, affect the fibres passing over in the commissure and produce dissociated loss of sensibility to pain, heat, and cold. It is still uncertain how far this gliosis is to be regarded as of primary, how far of secondary origin; what is particularly noticeable is the indication that this condition affords of the existence of tactile as distinct from other sensory nerves. In a considerable proportion of cases, tactile sensation is retained, whereas the senses of heat, cold, and pain are lost. It is held by some that the atrophy and necrosis of areas of the gliomatous new formation favor the occurrence of these cystic dilatations.

Circulatory Disturbances.—There is little that needs to be said regarding the circulatory disturbances of the cord as distinct from those of the brain. There may be **anemia** and **active** and **passive congestion** brought about by the same factors as in the brain. At most may be noted the occasional occurrence of elongated cysts, extending down the cord parallel with the still-extant central canal, which, according to Van Gieson, are of traumatic and hemorrhagic origin; they are, in fact, posthemorrhagic cysts. **Hemorrhage** may occur in purpura and the blood diseases, though it is usually a result of trauma. It has been suggested that the symptoms of "railway spine" are not purely functional, but

may be the result of multiple hemorrhages into the substance of the cord with subsequent cicatrization.

Inflammation.—Inflammation of the cord is known by the general term of **myelitis** and may be generalized throughout the cord or confined to certain local areas. It may again be divided into the form which affects the whole cord, or that affecting mainly the gray matter, **poliomyelitis.**[1]

Confusion exists as to what is truly called myelitis, in that the after-effects of a simple degeneration, such as that produced by compression, are indistinguishable from those following an acute (infective) inflammation. In the primary stage, these two conditions are quite distinct.

Myelitis, properly so-called, is the result of infection, or acute trauma, or both, and is characterized by definite reactive processes. It is found in acute general infections and in certain specific infections affecting especially the cord, preëminent among which is that known as acute poliomyelitis (see p. 236). Very important also are those forms in which infection occurs by extension, as in disease of the meninges, notably cerebrospinal meningitis, or of the vertebræ, as in caries. In all cases of true acute myelitis the affected portion of the cord appears pink, more hyperemic than normal, soft, so that it is almost impossible to cut it cleanly, and somewhat swollen. Microscopically, the main feature is a small-celled infiltration around the vessels, with evidences of degeneration, whether in the ganglia cells or the medullated fibres constituting the white matter. With this there may be an increased number of "granule cells" scattered through the affected area. The ultimate results are atrophy of the specific elements and a moderate degree of glial proliferation (sclerosis) with accompanying diminution in volume.

Regressive Changes.—Just as in the brain, so in the cord, with old age there is evidence of simple atrophy shown by diminished size, some shrinkage and pigmentation of the nerve cells of the gray matter, and, in addition, more particularly in the white matter, is to be recognized an increasing number of **corpora amylacea**, small corpuscles varying from 12 to 50μ in diameter, staining deeply with hematoxylin and the ordinary aniline dyes. These are specially numerous in the posterior columns. Whether they originate from glial cells or from degenerated medullated fibres is still a matter of uncertainty.

As already stated, acute degenerative changes result from **trauma, traumatic compression, hemorrhage,** and **infection;** more gradually produced degenerations may result from **tumors, gummas,** and **tuberculomas,** either in the cord itself or in the brain. It is more usual, however, to encounter the later stages of the degenerative process—secondary degenerations manifesting themselves by atrophy and sclerosis of one or more of the ascending and descending tracts in the white matter, and by shrinkage and, it may be, absence of cells and cell groups in

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[1] πολίος, gray; μυελόν, marrow.

the gray matter. Here the accompanying figure will recall the more important of the tracts, divided into the ascending and the descending, the long and the short.

We need merely recall that no matter what the nature of the cause, these secondary degenerations are all of the same order.

FIG. 293
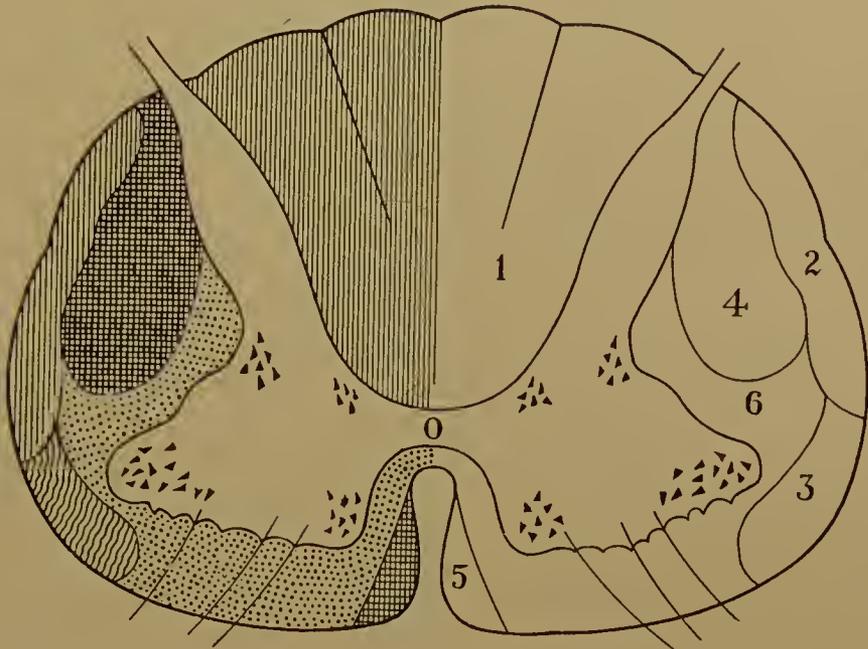
Diagrammatic section of spinal cord to show the more important tracts: 1, posterior columns (sensory and ascending); 2, direct cerebellar tract (sensory and ascending); 3, ventrolateral tract of Gowers (sensory and ascending); 4, lateral or crossed pyramidal tract (motor and descending); 5, direct pyramidal tract (motor and descending); 6, ventrolateral ground bundles.

FIG. 294

Tabes dorsalis. Dorsal cord, showing almost complete degeneration and sclerosis of the posterior (ascending) columns. (From the collection of Dr. Colin K. Russel.)

We are made aware of degeneration of this secondary nature by study of serial sections of the cord. During the development of the degeneration various special methods of staining, notable among which are Marchi's and Weigert's, pick out for us the affected fibres, largely in consequence of the chemical substances resulting from dissociation of the myelin of the medullated sheaths. Later, when the process of disintegration is complete, and the fatty matter has been absorbed, ordinary histological stains demonstrate, by their failure to color the tissue, that the axones and their sheaths have largely disappeared and

have been replaced by firmer, more translucent fibroid tissue, the out-
come of glial proliferation (**sclerosis**). These areas of degeneration
map out the geography of affected tissue, whether this be of the nature
of a degeneration throughout the whole cord, or an isolated area of
primary degeneration in the cord itself, with the tracts below or above
secondarily affected by that degeneration.

A degeneration throughout the cord, if descending, may result from
any lesion which separates these axones from their nutritive centre,
the nerve-cell body, or which destroys that nutritive centre, e. g.,
hemorrhage in the internal capsule or destructive lesion of the motor
cortex. Quite distinct from such lesions, but with the same ultimate
effects upon the fibre, are those scattered areas which arise appar-
ently at random in the cord and brain. They may arise from obscure
vascular causes as in multiple sclerosis, or from toxic causes as in the
posterolateral sclerosis associated with pernicious anemia.

As an example of these secondary degenerations, let us suppose that
the cord has been hemisected, that is, one-half of it has been cut through;
the knife has severed every tract and every longitudinally disposed fibre
in that half of the cord. The descending fibres that have been cut
show degeneration *below* the section, that is, special staining methods
will at first show these fibres in their state of degeneration, and later
their disappearance and replacement by sclerosis. The ascending fibres,
on the other hand, are relatively unaffected below the point of injury;
it is above this that the degenerations are seen.

Based upon these general considerations we may classify the main
diseases affecting the cord according to whether the lesions are due
to (1) destruction of the upper motor neurones; (2) injuries affecting
the axones of those upper motor neurones during their course down the
cord; (3) injuries of the lower motor neurones (diseases of the axones
of these, the peripheral nerves, will be considered separately), and (4)
diseases or injuries affecting the sensory neurones from the posterior
ganglion upward, and (5) diseases affecting motor and sensory neurones
coincidently.

It seems necessary in a work of this scope to leave out the great
mass of clinical detail that is involved in any full discussion of these
various spinal disorders; we can merely indicate the different types with
outstanding examples.

1. *Diseases Affecting the Cranial Distribution of the Upper Motor Neu-
rone.*—**Congenital spastic paraplegia** is a well-marked condition in which
nerve-cell bodies in the cerebral cortex have been destroyed, usually
by trauma at birth or again by obliteration of cerebral vessels during
foetal life, as in **congenital porencephaly.** Similar spastic paralysis of
like origin, namely, through destruction of cortical nerve cells, may be
of postnatal origin, due, for example, to the presence of **tumors, infective
granulomas,** or vascular obliteration (**acquired porencephaly**). As regards
the cerebellar neurones, the ideas of many authorities compel us to
include here **Friedreich's ataxia** as owing its most important symptoms

to an atrophy of nerve-cell bodies in the cerebellum. In this rare familial disease it must be remembered that there is also a spinal lesion of both motor and sensory systems.

Perhaps the commonest of lesions in the cord, secondary to primary insults in the brain, are those following upon **cerebral hemorrhage** and **cerebral thrombosis**. Hemorrhage affects most frequently the internal capsule and the pons, destroying axones of only one side of the body. In **multiple sclerosis** with its sporadic, irregular distribution of sclerosed areas of primary degeneration, either the cortex or the cranial tracts may chance to be involved, and so lead to secondary degeneration in the motor tracts of the cord.

2. *Disease Affecting the Axones of the Upper Motor Neurone during Their Course Down the Cord.*—The broad effects of such diseases are identical with those of the previous category; we make the separation because here the disease acts within the cord. Strictly speaking, we must here include conditions of **myelitis** diffuse or localized, because these affect the motor tracts, although it rarely happens that the effects are confined to these descending axones. Lateral sclerosis is a primary symmetrical sclerosis of both crossed pyramidal tracts, characterized by spastic paralysis without atrophy of the muscles, and by increase of the tendon reflexes. Although the main lesions are seen in the cord, it is really an abiotrophic condition of the whole motor neurone, and thus strictly might have been included with equal justice among the diseases of the upper motor neurone in the brain. This lateral sclerosis is seen in the **family type of lateral sclerosis** and **amyotrophic lateral sclerosis** (where the lower motor neurone is also affected). Pure examples of this condition are rare. As in the previous class, **multiple sclerosis** may happen to involve the motor tracts at any level and induce a secondary sclerosis below, with spastic phenomena; so also with **tumors** and the **infective granulomas**.

3. *Diseases or Injuries Involving the Lower Motor Neurones.*—In **bulbar paralysis** we deal with a destruction of lower motor neurones situated not in the horns, but in the bulb; the fact that the axones of these cells may run in cranial nerves, does not affect the principle that, although we are here dealing with diseases of the spinal cord, we have in bulbar paralysis a lesion of the nerve cell body of the lower motor neurone and its axone. The progressive atrophy of these neurones involves the nuclei of the hypoglossal, glossopharyngeal, the vagus and the spinal accessory nerves, and occasionally the motor nucleus of the trigeminal. We may repeat that such paralyses of lower motor neurones are flaccid, not spastic. Passing to the cord itself, the most extreme destruction of the lower motor neurones is seen in **acute poliomyelitis**. This is an infective disorder, characteristically of childhood, involving particularly the anterior horn cells, and leading, in a short time, to a flaccid paralysis, followed by atrophy and contracture of the paralyzed member. It is well to remember that in this disease, the inflammatory process is not confined to the anterior horns, but may affect the entire cord;

a cellular infiltration is seen along all vessels, most marked where the vascularity is greatest, viz., in the anterior horns.

Here again must be mentioned myelitis of the various acute forms, which obviously affects the nerve-cell bodies of the gray matter at the level concerned; as well as the gliosis of syringomyelia, **multiple sclerosis, tumors,** and the **granulomas.**

Another specific disorder specially involving the anterior horns and their nerve cells is the spinal form of **progressive muscular atrophy** (type Aran-Duchenne). In this the whole lower motor neurone undergoes atrophy and with it the innervated muscles. This disease affects those of middle age, is slowly progressive over years, and appears in some cases to be the result of a toxemia acting in the subject of abiotrophy (see p. 265), affecting particular groups of lower motor neurones. In **amyotrophic lateral sclerosis** there is also degeneration of the lower motor neurone; this has already been considered.

4. *Diseases Affecting Primarily the Sensory Neurones.*—Here, first and foremost, is to be recognized **tabes dorsalis** or **locomotor ataxia.** The characteristic lesion is an ascending degeneration affecting the posterior columns; in short, this is a sensory neurone disease; as to the cause of it, the Wassermann reaction has proved conclusively that nearly all cases are of syphilitic origin.

Regarding the exact nature of the process bringing about the degeneration, opinions are still divided. Considerable attention has been paid of late years to the degenerative changes seen in the posterior root ganglia, but it is now generally accepted that these are not sufficient to explain the extensive degeneration found in the posterior columns. So, also, certain observers have called attention to localized meningitis with thickening involving the meninges of the posterior aspect of the cord, and have assumed that the contraction of the fibrous tissue around the entering posterior root fibres is sufficient to cause an ascending atrophy and sclerosis. We are inclined to accept the view of Mott that the syphilitic virus affecting the vitality of the sensory neurones may cause a degeneration that first shows itself peripherally, and only with its progressive advance brings about a final atrophy of the nerve-cell body. It might be suggested that we deal with a selective action of the syphilitic virus telling particularly upon the sensory neurones; there are, however, indications that this view is incorrect, that syphilis induces a general lowered vitality of all the neurones; thus in those showing the early stages of tabes and accustomed to particular recurrent muscular movements (polishers and the like) a frequent symptom of the disease is paresis and wasting of the muscles involved in these movements. The reason why in the cord the sensory system is particularly involved appears to be that in the maintenance of muscular tone, etc., these neurones are in a state of continuous activity, whereas the anterior motor neurones, acted upon as they are from two sources, viz., from the brain and from the cord (in reflex action) have a period of comparative rest during sleep when the cerebral

stimuli largely cease to act. If the vitality of both orders of cells be depressed, the sensory neurones are more liable to become exhausted than are the motor.

Again, as in all the foregoing groups, **multiple sclerosis**, **myelitis**, **tumors**, **gummas** and **tuberculomas**, acting on some portion of the posterior columns, may lead to a secondary ascending degeneration.

5. *Diseases of the Spinal Cord Affecting Motor and Sensory Fibres.*— Here we have to take into account all those disturbances of the spinal cord which result in destruction with subsequent sclerosis of both ascending and descending tracts. Such are all those that affect the whole cord or all the substance of half the cord, such as the form above mentioned of **myelitis**; such, also, may be any of the lesions, more or less accidentally placed, such as **tumors** or the **granulomas**. It must be remembered also that in diseases which we commonly regard as diseases of one system, a certain proportion of cases may show an implication of a second system; thus in tabes dorsalis, when the brain is involved giving rise to general paresis, there may be a sclerosis of the lateral (motor) tract as well. Where, as in **multiple sclerosis**, numerous areas of primary, localized destruction of the spinal tissue have their origin, not so much in connection with tracts as with vessels, which in their course may pass through several tracts, there necessarily we encounter combined sclerosis, that is, a sclerosis of both motor and sensory tracts coincidently. In **Friedreich's ataxia** there are found atrophic tracts both ascending and descending (posterior and lateral columns, direct cerebellar, etc.). A similar state is found in **subacute combined sclerosis**, associated with pernicious anemia. Besides these, in **lathyrism** and **pellagra** are found similar states of combined sclerosis; the former of these follows the poisoning by several kinds of vetch (lathyrus), and the latter is commonly attributed to a diet of mouldy maize, though there is still much discussion upon this matter of causation.

Progressive Disturbances.—Associated with the low regenerative powers of the nervous tissues hyperplastic changes in the cord are distinctly rare. As regards the tumors, the **gliomas** are the only ones sufficiently common to deserve note. These gliomas originate most often in the immediate neighborhood of the central canal, and frequently are diffuse, being of the nature of gliosis rather than sharply defined glioma. If the central glioma breaks down, a condition of syringomyelia is produced.

THE MENINGES, CRANIAL AND SPINAL

The Dura Mater

Circulatory Disturbances.—The most important circulatory disturbances of the dura are **thrombosis** and **hemorrhages.** With the dura are

necessarily to be included the remarkable sinuses of the cranium, for these are formed in the substance of the dura; by their situation and course they are peculiarly liable to be the site of thrombosis, rather from the skull than from the firm, resistant dura itself.

Thrombosis.—Thrombosis may be **traumatic, marantic,** and **infective.** The marantic form is occasionally met with in cases of chronic exhaustive diseases associated with cardiac weakness and slowed circulation, and is most often met in the longitudinal sinus. It is by no means clear that this, and the somewhat allied form occasionally seen in chlorosis, may not be due actually to infection of a low grade. There is some tendency now to regard all non-traumatic thromboses as infective. Infective thrombosis, especially of the lateral sinus, is the most important of all these conditions, and most often arises by extension from inflammatory processes in the mastoid cells, either directly or by way of the emissary veins in the petrous bone or in the cranial vault. The cavernous sinus is less often thrombosed by extension from the orbit or elsewhere. The sinus is distended by a clot, grayish-pink to dark red, firm or softened according to its duration, and at times even appearing as little else than a purulent mass. Such a sinus thrombosis may spread to a surprising extent into other sinuses, and into the jugular veins. The results of this softening are very frequently the development of multiple abscesses in the lung and pyemia, not to mention the more local development of meningitis and cerebellar and cerebral abscesses.

Hemorrhage.—It will be recalled that the arteries run on the external aspect of the dura; thus while there may be small capillary hemorrhages in the substance of the dura, any large hemorrhage brought about by traumatic or other rupture of branches of the anterior or middle meningeal arteries, is situated between the dura and the skull; despite their extradural position, such may naturally bring pressure upon the underlying brain substance (**cephalhematoma internum,** contrasted with **c. externum,** under the scalp). Subdural hemorrhages originate from the vessels of the pia-arachnoid. The same principle obtains, *mutatis mutandis,* in connection with the spinal dura.

Inflammation.— **Acute Pachymeningitis Externa.**—This inflammation of the outer surface of the dura is practically always secondary to infection of the skull, the sinuses, or the vertebræ, or follows infected wounds; it may be of any degree up to abscess formation, and, by the firm connection between dura and bone, is localized, since extension is only obtained at the price of stripping off the adherent dura or burrowing into the resistant bone.

Pachymeningitis.—It is not a little interesting to note that inflammation of the pia-arachnoid may progress with little evidence of involvement of the dura, while contrariwise, the curious condition, **pachymeningitis hæmorrhagica interna,** affords at least in its early stages a picture of involvement of the dura alone. In this relationship or want of relationship we may recall that the blood supplies of dura and pia are from entirely different sources, and presumably thus, in connection

with inflammation, the infection may travel by one and not by the other. In pachymeningitis hæmorrhagica interna the earliest stage so far recognized is that of areas of the inner surface of the dura covered by a thin layer of fibrin. What is the cause of this phenomenon we do not know, but we suppose that there has been a hemorrhagic oozing of exudate from the finer capillaries of the dura. The conditions in which this is found, viz., in alcoholics and the insane, does not help us to determine the etiology. Studies of cases of longer standing give evidence that with the organization of this first deposit the newly formed capillaries, originating from the dural vessels, again afford a hemorrhagic exudate, which once more exhibits fibrin formation and organization, and in this way in the course of months, there develops a thickened layer of new tissue which may attain considerable depth, and by its pigmentation indicate that there have been recurrent hemorrhages. The outer side of the dura is not affected. This layer of new tissue may extend over the larger portion of the dural lining of the skull, and in many cases may show little evidence of extension of the inflammatory process into the pia, there being no adhesions to the underlying brain substance, though in other cases these adhesions are so extensive and close that it is impossible to think that the pia has not entered into the process, even if secondarily. Whether pachymeningitis is truly inflammatory must be left an open question.

Pachymeningitis Cervicalis Hypertrophica.—This disease attains importance only because it may lead to so extensive a thickening of the structures around the cord in the important cervical region, that the nerves are implicated and compressed as they leave the cord. The new-formed layers may extend as a collar, three or four inches wide, and very thick, around the cervical cord; the cord may be so compressed that degeneration occurs, and the vessels so obstructed that the cord softens. The general opinion is that this is a syphilitic manifestation; it may require years to develop, with periods of quiescence.

Tuberculosis.—This arises chiefly from tuberculosis of the pia-arachnoid, or of the bone; the latter is more common in the cord by extension of Pott's disease. There may be gross conglomerate tuberculosis or miliary tubercles.

Syphilis.—This may appear as gumma or as a diffuse process, and may be an extension from disease of the pia-arachnoid or from gummatous caries of the skull or vertebræ; this latter condition, thanks to better treatment, is today rare.

Progressive Changes.—Tumors.—These are essentially of the connective tissue and endotheliomatous type. The so-called **osteomas** of the dura are, strictly speaking, osteophytes, showing no inherent tendency to grow; they are plaques of osteoid tissue of metaplastic origin from the connective tissue. **Chondromas** are rare. Pure **fibromas** are at times recognized, but the small benign tumors, solitary or multiple, attached by a broad base to the inner aspect of the dura, are strictly **endotheliomas**, originating apparently from the endothelial

inner layer of this membrane. In general these are firm and on section exhibit a framework or stroma of fibrous tissue in the meshes of which are more or less abundant cells of endothelial type, arranged concentrically after the type of the endothelioma proper. Whether the fibrous tissue is truly a stroma or is to be regarded as a metaplastic change of the endothelial cells is debatable. On section through these tumors, they have a "sandy" feel, and microscopically, there are found more or less abundant globular bodies with concentric striation, calcified. These are the **psammoma** bodies, and when this particular form of degeneration is present, the tumor as a whole is called a **psammoma**. This, to repeat, is an endothelioma with calcification of its more central necrosed cells.

Apart from these small firm tumors, we occasionally find larger, more cellular tumors, up to the size of an orange or larger, which are more purely endotheliomatous, or have the characters of a round-celled **sarcoma**; or again, we find diffuse growths of either endotheliomatous or sarcomatous nature spreading over a large area of the inner aspect of the dura. These larger growths naturally compress and produce atrophy of the underlying brain substance. Pure sarcomas do, of course, arise from the subendothelial part of the dura, and these are usually spindle-celled.

There may be *secondary* sarcomatous and carcinomatous tumors affecting the dura mater; this secondary involvement is probably more common in the spinal than the cranial dura, and it has been observed that mammary **carcinomas** are liable to afford metastases either into the vertebræ or directly into the dura, which growing are apt to fill the spinal canal and compress the cord.

The Pia-arachnoid

Anatomically a distinction is made between the arachnoid and pia; pathologically no such distinction can be made; in other words the pia-arachnoid may be regarded as a loose, abundantly vascular membrane (covered on its dural aspect by a simple layer of cells) in the meshes of which are abundant and large spaces lined by endothelium, the arachnoid spaces, and in these spaces there circulates the cerebro-spinal fluid. The vessels of this membrane give off branches which penetrate the brain substance, and it enters the ventricles as the choroid plexuses.

Circulatory Disturbances.—**Anemia** is brought about in a general or a local way, the latter as in hydrocephalus internus. **Active hyperemia** is not easily recognizable, because the richness of the vascularity of the brain in the corpse is so variable, the blood easily draining away if the thorax has been opened before the cranial section. **Passive congestion** leaves its marks through the dark bluish color of the congested vessels. **Œdema** is not uncommon; it may be complementary (**hydrops ex vacuo**), where there has been atrophy of the brain substance, or

congestive, as in the newborn in cases of prolonged labor with head presentation, or hydremic as in nephritis, or inflammatory, associated with acute infections. **Hemorrhage** may be traumatic or may occur in the hemorrhagic diseases, in rupture of aneurysmal dilatations of the vessels, or in severe infections; blood may appear in the arachnoid spaces by extension of hemorrhage from the brain substance.

Inflammation. — Leptomeningitis.—This may be serous, fibrinous, purulent, or a combination of these; or in more chronic infections, tuberculous or diffuse, as in syphilis.

Acute leptomeningitis.—The **serous** form is characterized by the inflammatory œdema just mentioned; it is seen particularly in young individuals as the result of acute infections; at times the rapid accumulation of the fluid leads to pressure symptoms and even to optic atrophy. It is also seen as an early stage of cases that are destined to become purulent. More striking and more severe in their effects are the different forms of **suppurative meningitis.** Many agencies can cause this, notably the meningococcus, pneumococcus, strepto- and staphylococci; bacillary forms are not so common; influenza is perhaps the most frequent, B. typhosus, B. pyocyaneus, B. coli and several others are occasionally recorded as leading to this disease. Such infections may be either hematogenous or by extension along the lymph spaces, as from the middle ear, the nasal passages, the orbit, etc. Up to a few years ago conditions like epidemic cerebrospinal meningitis were held to be idiopathic; an increasing amount of proof today indicates that they are secondary to growth of the specific organisms in the upper nasal passages. There are two areas which are especially liable to be the seat of purulent accumulations, viz., the base of the brain from the foramen magnum forward, and the vertex, over one or both hemispheres. The pus is specially apt to lie along the superficial vessels, in the sulci, but may be so abundant as to form a thick layer hiding all the convolutions of the hemispheres. In general, owing to free communication along the arachnoidal spaces, this purulent fluid extends down the cord, where it is apt to accumulate along the anterior and posterior fissures. The ventricles, also, may be similarly invaded by extension along the choroid. A local meningitis may arise either by extension from without, as in mastoid disease, or from within the brain, as in abscess. It may be laid down that through the intimate connection of the vessels with the cortical substance, the outer layers of the gray matter are apt to be involved, so that we deal more often with **meningo-encephalitis** than with pure meningitis. It · is to this involvement that we owe the pareses and other nervous phenomena that present themselves after the acute attack has passed by.

All forms of meningitis, save perhaps the syphilitic, are more liable to attack children than adults; this is notably the case with the epidemic and the tuberculous forms.

Chronic leptomeningitis presents itself as a milky thickening of the meninges in the immediate neighborhood of the superficial vessels

over the convexity and again by a translucent, gelatinous material at the base of the brain; further, especially in the old and the alcoholic, the opacity over the ventricles may become more diffuse, and yet more rarely, as the remains of an old acute inflammation, there are to be encountered definite fibrous adhesions between the dura and pia-arachnoid.

Tuberculosis.—One of the commonest forms of meningitis, and then often running a relatively acute course, is the **tuberculous.** This shows itself most frequently as manifestation in part of a general hematogenous miliary tuberculosis, and is recognizable on careful examination by the presence along the vessels of the Sylvian and other fissures and of the choroid plexus of minute pinhead and smaller tubercles, which become apparent if a small piece of the arachnoid be floated out in water and examined with a hand lens. Other favorite sites are over the pons and on the apposed surfaces of the cerebellum and the temporo-sphenoidal lobes. More rarely the tubercles instead of being generalized may be few in number over a small area, *e. g.*, of the cerebrum. This appears to be an early stage of the cerebral or cerebellar tuberculoma. While the superior surface may appear relatively healthy and free from diffuse inflammation one may discover on lifting the brain, that all the interstices at the base are filled by a yellowish, gelatinous translucent and œdematous mass, really the swollen and infiltrated pia-arachnoid. In general, the basal areas are the most involved, and it is to be remembered that in practically all cases, there are here not only the miliary tubercle, but signs of exudation and increased presence of lymphocytes in the earlier stages, and of large mononuclear cells in the later stages.

Syphilis.—Localized gummas of small size may be formed in the meninges of the base, part of a greatly thickened matting of the arachnoid, in which the individual gummas are not to be distinguished by the naked eye. The solitary gummas may, however, be recognized by their yellow, caseous centres. More typical of cerebral syphilis is the diffuse thickening of the basal meninges, with firm adhesion to the brain substance, and thickening along the basal nerves. This process of syphilitic infiltration around the vessels, with possible subsequent gummatous formation is liable to extend into the brain substance (see p. 582). Rarely, the only sign of syphilis in the cranium may be a localized peri- and mesarteritis of a single superficial vessel.

Progressive Changes.—Small plates of metaplastic ossification occasionally are to be met in the leptomeninges as in the dura.

Tumors.—Rarely among the benign tumors are to be encountered the **lipomas, cavernomas,** and **lymphangiomas,** as also **fibromas.** More common and more characteristic are the primary **endotheliomas.** These are of two main types: the more frequent is composed of whorls of concentric, flattened cells, and these must be regarded as **hemangio-endotheliomas;** the other form shows cells of a more cylindrical type and peritheliomatous arrangement. These, it is supposed, are strictly **lymphangio-endotheliomas.** Both forms are apt to show transitions

into more purely sarcomatous growths, though occasional pure round-celled **sarcomas** are to be met. An unusual tumor found especially in connection with the pia mater is the true **cholesteatoma,** in no wise to be confounded with the cholesteatoma found in the middle ear. These tumors form pearly, multinodular masses, occasionally reaching the size of a small apple. They are found originating in the pia, particularly at the base in the region of the pons and medulla, and occasionally over the cerebellum, choroid plexus, or cord. They are to be regarded as **inclusion dermoids,** which subsequent to their inclusion have taken on blastomatous growth. The cells composing them are of epithelial nature, containing keratohyaline granules; the pearly appearance is due to inspissated cellular debris containing fat and plate-lets of cholesterin. More than one observer has found hairs in these, and sebaceous glands have been detected.

PERIPHERAL NERVES

The peripheral nerves may be divided into two systems—the somatic and the sympathetic; the former are composed entirely of medullated nerves, and have a somatic distribution to the voluntary muscles and skin; the latter are composed of fine medullated and of non-medullated nerves; their fibres innervate the non-striated muscles of the body, including those of the blood vessels and the intestines, the various glands proper, and the striated muscle of the heart. The arrangement of the latter system is distinctly complicated and must be studied in the more recent text-books of anatomy. It is due especially to the work of Prof. Langley that our knowledge of the anatomy of this system has been elaborated. Briefly we may say that the non-medullated efferent fibers take origin from the lateral horns and pass out by the ventral roots to a series of vertebral ganglia, where either they end, or passing through, are distributed to a second group of ganglia, the prevertebral. Not every segment of the cord gives origin to these fibres, but we may distinguish a cervical group in connection with the superior cervical ganglion, a main group originating from the first dorsal to the second or third lumbar and a third series originating from the second, third, and fourth sacral.

This sympathetic system we may rapidly dismiss; experiment and pathological anatomy have afforded us singularly little clear-cut evidence with regard to either the diseased conditions that may affect it or the results of its destruction. While some observers describe an important series of disturbances following removal of the solar plexus, others have kept dogs alive for several months after this operation, with very little bodily disturbance. We point out again that the afferent sympathetic fibres convey impulses which under normal conditions do not reach consciousness, although, under certain circumstances, their irritation stimulates other ganglion cells, impulses from which

affect consciousness, and as a result irritation of the sympathetic is
referred to areas of the somatic innervation. We have referred, also,
to the relationship between the sympathetic system and the medulla
of the adrenals. Thus, Wiesel describes degeneration of the chromaffin
cells of the sympathetic ganglia in Addison's disease, cells identical
in character with those found in the adrenal medulla. We can, that is,
produce isolated examples of evidence of sympathetic activity and its
disturbance, but we are not prepared as yet to formulate any general
statements.

Inflammation.—The term **neuritis** is very loosely employed. While
there are examples of true inflammation, frequently this term is used
to indicate atrophic changes. Thus, the so-called optic neuritis is
better referred to as **choked disk.** It is a disturbance of the optic
nerve, leading to atrophy, brought about by intracranial pressure and
obstruction of the vessels, with associated œdema. Similarly, **alco-
holic, arsenic,** and **lead neuritis** are degenerative rather than inflammatory
states. In genuine acute neuritis the peripheral nerve trunks affected
are swollen and congested, not necessarily along their whole length but
for a longer or shorter distance, so that they may present spindle-like
swellings along their course. In such cases, there is an exudation
into the connective tissue of the sheath affecting the endo-, peri-,
and epineurium. With this there may be more or less leukocytic
infiltration, so extreme that there may at times be actual pus formation
with or without localized hemorrhages, and where the inflammation
is intense the action upon the nerve fibres leads to breaking-up of
the medulla and also of the axis cylinders. Purulent inflammation
of nerves usually occurs by extension from neighboring tissue. Such
acute neuritis may be followed by connective-tissue overgrowth, which,
in its turn, by pressure, favors degeneration and atrophy of the included
axis-cylinder processes. Such neuritis, besides being of infective origin,
may be traumatic, from wounds or compression.

One of the **infective granulomas** stands out preëminently in its liability
to affect the peripheral nerves—**leprosy.** Numerous peripheral nerves
of the limbs, face, and other regions become involved by granulomatous
growth, rich in "lepra cells" containing the bacilli, and bring about
anesthesia, pallor, and atrophy of the regions of supply, so that fingers
and toes undergo a form of dry gangrene and drop off, leaving extensive
scars. The later stage of this chronic process in the nerves is seen
as fusiform fibroid thickenings along their course. **Tuberculosis** of
peripheral nerves, while it occurs with similar distal degeneration is
comparatively rare. Until salvarsan came into frequent employment
the effect of **syphilis** upon the nerves was overlooked by most path-
ologists, but syphilis is now held responsible for a large number of dis-
turbances of the optic and auditory nerves which may appear after the
use of salvarsan and more rarely of mercury. The attention drawn
to this subject has shown that lesions of these two nerves are not
uncommon in the course of untreated syphilis.

Regressive Changes.—Here must be included many forms of so-called neuritis from alcohol, arsenic, lead, ergot, diphtheria, beri-beri, and the presumed causative toxins of severe anemias, to mention the more important. Many of these toxic agents have a characteristic selective activity. Thus the diphtheria toxin leads to areas of acute degeneration and atrophy, picking out certain nerves in the upper respiratory tract, as well as the vagus, the degeneration of the latter being the cause of sudden heart failure. Lead affects the innervation of the extensor muscles of the forearm and leg, causing **wrist-drop** and **foot-drop.** Alcohol may set up a widespread polyneuritis, especially affecting the peroneal nerves. In all the above the degeneration of the peripheral nerves appears to be **primary,** they being directly affected. What is termed **secondary degeneration** is seen in the peripheral nerves whose cell bodies have previously undergone destruction, or which have been cut off from those cell bodies, as in true Wallerian degeneration.

Progressive Changes.—We have already referred (see p. 362) to "false neuromas" or amputation neuromas, as also to what we have termed **neurinomatosis** or **multiple neurofibromas** or **fibromatosis** (see p. 346). The so-called **elephantiasis neuromatosa** or **pachydermatocele,** appearing as a congenital affection, has underlying it a great irregular thickening of the nerves, of the same order. Associated with this is a general deformity of the part with thickening of the skin. Rarely **gliomas** have been described as occurring along the course of peripheral nerves and still more rare are **lipomas** and **rhabdomyomas.**

All of the gliomatous and neurinomatous tumors show a tendency toward a malignant metamorphosis, the latter giving origin to spindle-celled, sometimes **myxo-sarcomas.** Of secondary tumors carcinoma has been described as occasionally extending in nerve bundles and bringing about atrophy of the same, but in general, nerves are little involved in secondary malignant growths.

THE EYE

Anomalies.—The eyeball may be lacking (anophthalmia), a state which is usually found in conjunction with other grave defects; occasionally there may be found tissues that represent the eyeball, and in yet other cases a small bulb may be present (microphthalmia). In different kinds of cyclopean monsters, two eyes in a single orbit or a single eye in a central orbit are seen. The cornea may be smaller or larger than normal, or its curvature may be more or less convex than normal; part or all of its substance may be opaque, usually in such states as microphthalmia. The iris may be **absent,** or may lack pigment (albinism); the lens may show **opacity,** or tissue strands on the surface may represent the remains of the hyaloid vessels; the lens may be **dislocated.** Any or all of these different parts may be lacking in **coloboma.**

Coloboma is a congenital failure of the cleft of the secondary optic vesicle to close, either wholly or in part. This may thus affect every or any part from the optic nerve to the eyelid; most often the part affected is the iris, and the defect is frequently associated with other congenital anomalies.

Circulatory Disturbances.—*Conjunctiva.*—The conjunctiva becomes **hyperemic** as a result of irritation from a foreign body, from irritant gases, from exposure to bright light and cold wind at the same time, as is seen in snow-blindness, from crying, from facial neuralgia, and as an early symptom accompanying rhinitis. **Persistent hyperemia** is well illustrated in the eye of the alcoholic subject, and occurs in most cases where there is constant **eyestrain**. **Œdema** of the conjunctiva (and of the soft tissues of the lids) is seen as an early stage of generalized anasarca in Bright's disease and broken compensation of the circulatory apparatus. A common cause of local œdema is the sting of an insect. **Hemorrhages** in the conjunctiva are the result of injury or arise during the effort of violent coughing or sneezing, especially in children with whooping cough.

Iris.—**Hyperemia** is of importance as an early accompaniment of inflammation.

Choroid.—**Hyperemia** is seen as an accompaniment of inflammation of the choroid and surrounding parts, and in its passive form, as part of a general congestion of the body in general or the head in particular. **Hemorrhages** in the choroid are due to trauma, and the hemorrhagic diseases.

Retina.—Circulatory changes seen in the retina are of a good deal of importance, especially because the function of sight is readily affected. **Anemia** is characterized by a visible narrowing of the arteries, with pallor of the membrane; if extreme, the nutrition of the retina may be affected and partial or total blindness result from its degeneration. **Hyperemia** occurs as part of an inflammation of the retina and of surrounding structures, or may be passive, as a result of general congestion. More important is that passive hyperemia seen in **choked disk**, where by compression of the central vein the retinal veins are larger and more tortuous than usual. **Embolism** of the central artery of the retina occurs occasionally, and sudden blindness with anemia of the membrane results; later, severe degenerations arise with ultimate destruction. **Thrombosis** of the same vessel is attended by similar results but is less frequent. **Hemorrhages** of the retina are of much clinical interest. They occur in systemic maladies such as Bright's disease, diabetes, and all those diseases which are characterized by capillary rupture— the anemias, the severe infections, scurvy, and certain other severe intoxications. They occur also in trauma, and fairly large areas of the retina may be lifted off the choroid (**subhyaloid hemorrhage**) with subsequent degeneration of the part with whose nutrition there is interference. Retinal hemorrhages vary in position, and consequently in shape and size. If superficial in the nerve fibre layer, they have a

striate form, if deep they are round or irregular. It will be readily understood that hemorrhages of the retina may be accompanied by escape of blood into the vitreous, with consequent dimness of vision.

Inflammation.—For an enumeration of the agents of inflammation, and their results on the different parts of the eye it is hardly necessary to mention that more voluminous works must be consulted.

Conjunctiva.—Apart from injury, exposure to bright light or irritating vapors, the use of drugs, such as potassium iodide and arsenic, inflammations of nearby or related parts, there are many bacteria which cause **acute conjunctivitis.** The readiness with which bacteria can gain access to the conjunctiva is self-evident; nowhere else in the body is so delicate a structure so exposed. In a considerable percentage of healthy conjunctivæ, the Bacillus xerosis and a non-pathogenic Staphylococcus albus are found. The bacteria which most often cause conjunctivitis are (in the order of frequency in a large series studied by our colleague, Dr. Hanford McKee), Morax-Axenfeld diplobacillus, staphylococcus, streptococcus, pneumococcus, Micrococcus catarrhalis, gonococcus, B. McKee, B. Koch-Weeks, B. coli, B. influenzæ, meningococcus, B. xerosis, B. Hoffmann—while a large variety of saprophytes is seen, many individuals of these last being found in greater frequency than some of the pathogenic microbes enumerated.

The character of the inflammation varies greatly but is in no way distinct from that described in vascular areas; catarrhal, purulent, and membranous forms are seen. The severe degrees of inflammation are apt to jeopardize the integrity of the delicate cornea; the chronic forms may lead to considerable superficial loss of conjunctival tissue, the healing of which may be attended by deformity of the lid. **Pterygium** is an inflammatory overgrowth of the conjunctiva upon the eyeball, of triangular shape, the apex directed to the pupil; sometimes it becomes quite well vascularized, and the superficial epithelium is proliferated and even at times folded.

Chronic Conjunctivitis.—The forms of conjunctival inflammation known as chronic are, in the main, characterized by proliferation of the tissues, which appear as granulations varying in size from those just visible to cock's-comb-like masses of large size. The so-called **trachoma** is the most important of these, the overgrowths being not typical granulations, but small encapsulated overgrowths of lymphoid and connective tissues. It has been shown that the so-called "trachoma bodies," intracellular bodies found in the epithelial cells in trachoma, are not the etiological factor. **Parinaud's conjunctivitis** is a rare but severe form accompanied at times by marked systemic disturbance. **Vernal conjunctivitis** is a malady of persistence, with annual exacerbations, in which the granulations are hard, composed of thickened epithelium and connective tissue, at times degenerated into a hyaline mass. The **infective granulomas** are rarely seen to affect the conjunctiva. **Tuberculosis** may spread from lupus of the face, and **syphilis** and **leprosy** are known.

Cornea.—The process of inflammation in the cornea (**keratitis**) has already been described (see p. 132); from what has been said there, it will be gathered that the collecting of lymph cells and the production of new corneal corpuscles will give rise to some opacity of the cornea, local or diffuse. This may be recovered from and the foreign elements be absorbed, but on the other hand, a certain opacity may remain, or the inflammation may become more intense, with loss of substance within or on the outside of the cornea. Should this loss of substance be repaired, the connective tissue which performs the repair may, on the one hand, remain as an opaque body, and, on the other, by its contraction alter the curve of the cornea, thus impairing its efficiency as a refracting body; vascularization of the surface of the upper part of the cornea may occur in trachoma, constituting **pannus**.

Diffuse parenchymatous keratitis, evidenced by infiltration of the cornea, may lead to vascularization in the *substantia propria*, the formation of new vessels being deep. Should loss of corneal tissue occur on the surface, **corneal ulcer** is the result, and if in the substance, abscess.

Suppurative keratitis may be **phlyctenular**, generally close to the corneoscleral margin, where minute pustules appear just under the surface, rapidly breaking through. A considerable number of cases of suppurative keratitis are due in part to the coexistence of injury.

Corneal ulcer may occur with inflammations of various intensity; it may arise in ill-nourished children and progress slowly, or it may be the result of a florid conjunctival inflammation and erode rapidly. The **serpiginous ulcer** is named from the fact that while the ulcer heals at one part of its edge it progresses at another; it is practically always due to pneumococcus.

Herpes of the cornea may occur, associated with marked anesthesia.

The **infective granulomas** are of considerable importance in the causation of keratitis; the diffuse form is frequently syphilitic, much less often tuberculous, but the localized occurrence of the gumma or the tubercle is rare. It was previously thought that there was a specific form of keratitis which followed lesion of the fifth nerve, but it has been shown that this is not neurotrophic, but due to infection because the eye is less protected than in health.

Iris.—Inflammation of the iris should always at once suggest to the beholder systemic disease, and in the order of frequency is due to syphilis, rheumatism, tuberculosis, gonorrhea, gout, diabetes, oral sepsis, and trauma—overwhelmingly the first two. Fibrinous exudation from the vessels of the iris blurs its bright surface, and with this exudate there exists a strong tendency to adhesion (**synechia**) to the capsule of the lens behind it. The inflammation may not present the fibrinous form but may be frankly suppurative, the pus lying in the anterior chamber (**hypopyon**); this usually follows a wound that has perforated the cornea. The **granulomas** exceptionally show the **gumma** and the **tubercle**, usually being represented by diffuse plastic exudations; sometimes in the case of syphilis, small yellow nodules are seen at the

pupillary edge, which in late cases only, are to be regarded as true gummas.

Ciliary Body.—**Cyclitis**, inflammation of the ciliary body, is often combined with iritis, the combined disease being **iridocyclitis**. The symptoms are those of an iritis with the addition of excessive pain, tenderness in the ciliary region, an increased or a decreased tension, and considerable disturbance of vision. There are different varieties, the **simple**, the **plastic,** and the **purulent**. The plastic form, characterized by the presence of fibrinous exudate, arises from an injury in the danger zone, and is important because of its ability to set up a plastic iridocyclitis of the other eye, *i. e.,* **sympathetic ophthalmia.** Such a plastic cyclitis, if not checked, will destroy the eye by atrophy of the eyeball. The sympathetic ophthalmia may arise weeks, occasionally years after the onset of cyclitis in the eye first affected, and as to the mode of transmission of the infection, a century has not added any certainty to our knowledge. Purulent cyclitis, or better, iridocyclitis, results from injury, and the infection sets up **panophthalmitis.** In this grave state, there is suppuration and disintegration of all the soft internal structures of the eyeball, generally accompanied by severe inflammation of the conjunctiva and the soft tissues of the orbit. The inflammatory products may greatly distend the eyeball, their escape being prevented by the dense sclera, which in time may be itself eroded to the bursting point, when the contents escape. Should the eyeball not be removed there may be a gradual shrinking of the empty sac, and a more or less solid mass of firm tissue be left to represent the globe (**phthisis bulbi**).

Choroid.—**Choroiditis** is caused by systemic disease, syphilis, tuberculosis, certain disorders of nutrition, or a bacteriemia; in other cases the cause remains undiscovered. Sometimes in the granulomatous infections, and always in the bacteriemic, it appears as an **exudative** or a **purulent** inflammation. These terms sufficiently explain themselves; the exudate may remain upon the choroid or may be thrown out into the vitreous which loses its transparency for the time being; even a mild grade of choroiditis may, in healing, be followed by atrophy. A suppurative choroiditis, as stated above, is almost necessarily a forerunner of panophthalmitis.

By reason of the propinquity of the retina, this membrane is practically always affected; in the acute type, the retina quickly disappears, but in the more slowly progressing infections, the retina shows changes peculiar to it, and the disease is known as **choroidoretinitis.** In tuberculosis, tubercles of miliary size are seen in the choroid, lifting the retina, or larger aggregated caseous masses may be found; the retina is cloudy and loses its distinctive features as a result of œdema or exudation, combined with degeneration of its individual structures. Syphilitic choroidoretinitis is seen as a localized or diffuse process, the choroidal proliferation being sometimes extensive.

Retina.—**Acute retinitis** arises by extension of infection from any of the above-mentioned parts. In this condition, the retina is congested, œdematous, and cloudy. Apart from these cases, a like appearance is seen, indicative, not of an acute local infection, but of a systemic state such as Bright's disease, diabetes, syphilis, or arteriosclerosis, the last named indicated by hemorrhage. Most important of retinal changes is that known as **albuminuric neuroretinitis**, a description of which will in general serve for the changes seen in any of these bodily states. Not infrequently the retinal examination, undertaken because the vision is failing, gives the first alarm of the existence of the disease. There are swelling, cloudiness, and lack of definition of the papilla; the retina shows points, streaks, or flame-shaped areas of hemorrhage, and there are in the macular region irregular whitish areas formed by the accumulation of cellular debris which has undergone fatty, granular, or hyaline degeneration. Withal, there is lymphocytic and fibrinous exudation into the retina, whose vessels appear engorged and tortuous. The coexistence of the hemorrhages and the whitish areas marks the state of neuroretinitis. Whether due to Bright's disease, diabetes or a transitory albuminuria of pregnancy (**gravidic neuroretinitis**) the picture may be the same, but the subsequent course of the process may be quite different; in the last named, the retina may recover with the disappearance of the albuminuria after labor.

When due to syphilis, the lesion is that referred to above, choroido-retinitis; it may be congenital or acquired, and appears in the so-called second stage of syphilis, usually in both eyes. The fundus is indistinct, the retina and the disk are swollen, and fine, dust-like opacities (cast-off exudate) appear in the posterior part of the vitreous. In the **hemorrhagic** form, so-called because the hemorrhages are abundant, the usual signs of retinitis are present, and, in addition, there is a series of recurrent hemorrhages, the whole often being an indication of widespread vascular disease (arteriosclerosis), and a forerunner of cerebral hemorrhage.

Regressive Changes.—The only regressive changes of importance are those observed in the cornea, the choroid, the retina, and the lens.

Cornea.—In the first, the cornea, there is a regressive change which is called **arcus senilis**. It consists of whitish arcs that are seen at the margin of the cornea above and below, ultimately joining, made up of very minute drops of fat which lie in the substance of the cornea as far posteriorly as Descemet's membrane; sometimes the whitish tissue appears to be a kind of hyaline, while in other cases there appears to be a deposition of lime salts in the transparent tissue of the cornea, which deposition the advancing degeneration of the blood vessels favors. It is thus little more than a sign of arterial age. In the *choroid*, sometimes as a sequel to previous inflammation, areas of atrophy occur, with irregular pigmentation, and sometimes ultimately even the production of bone. In the *retina*, degenerative changes occur as the result of age, as well as after various forms of disease, such as retinitis and

subretinal hemorrhage. The rods and cones may atrophy, or undergo obscure fatty or other changes. Cysts may arise, and the amount of pigment may increase or decrease. Those cases of separation of the retina in which the superficial layer comes away leaving the pigment layer attached to the choroid are naturally accompanied by grave changes in the separated layer, which becomes œdematous and may undergo maceration or degeneration of different kinds, even to the deposition in it of calcareous material.

Retinitis Pigmentosa.—This is strictly a regressive and not an inflammatory state of the retina, which occurs in particular families, affects males, especially those who are the offspring of consanguineous parents. In this rare disease, the retina is degenerated and atrophied, and there is a migration or a carrying of the pigment from the external layer, where it normally lies, to the inner layers of the retina, where it is deposited. We have previously pointed out that the pigment-carrying cells of the skin seem to have migratory powers; it is not possible to say by what method the pigment changes its situation in retinitis pigmentosa, but it is laid down apparently in endothelial cells in the vicinity of blood vessels in fibrotic areas.

Lens.—The regressive changes in the lens that are of importance are those that give rise to opacity—in short, the various forms of **cataract.** Cataract is of two distinct forms—**stationary** and **progressive.** In the former, a corneal infection may lead to a localized area of opacity on the anterior surface of the lens which remains through life, but which is of little importance, because it does not increase in size. A like condition may affect, though more rarely, the posterior surface, or a single lamella in the lens may be opaque, and of this the extent and importance are necessarily greater. Progressive cataract is (1) senile, (2) congenital (juvenile), and (3) traumatic. In senile cataract, the most familiar form, the fibres of the lens undergo degeneration with the formation of fatty globules and myelin. Usually the opaque lens has to be removed by "extraction." It may happen, further, that after such a lens has been removed, the posterior capsule, which has, of course, remained, may itself become opaque—**secondary cataract** —and this opacity constitutes **capsular cataract.** In traumatic cataract the lens is opaque as a direct result of an injury, and here it is that a considerable degree of absorption of the opaque tissue may occur; should the lens fibres become separated and fluid be absorbed (from the aqueous) the lens may swell up, may become soft, and may even be completely absorbed. If the lens and capsule become fixed to some nearby structure and vascularized, a considerable fibrous proliferation may occur, and this, together with the new blood vessels, constitutes a very great detriment to the transparency of the lens. Even calcareous material may be ultimately deposited.

Progressive Changes.—*Conjunctiva.*—Certain benign tumors, **fibroma, lipoma, papilloma,** or **osteoma** are found on the conjunctiva, but the most important are malignant—the squamous **carcinoma** and the

sarcoma. **Carcinoma** is oftenest seen as an extension from the eyelid or other nearby structure. **Sarcoma** is less common, and when it occurs, may be of the pigmented variety.

Cornea.—Primary tumors of the cornea are very rare. Isolated cases of primary **fibroma, papilloma, sarcoma,** and **myxoma** are in the literature. The structure may be secondarily invaded from other parts of the eye.

Iris.—Pigmented **sarcomas** are found, but by no means so commonly as similar tumors in the choroid.

Choroid.—The most common progressive tissue change in the choroid is **melanotic sarcoma,** of which, indeed, it is the most frequent site. These tumors are markedly pigmented, consist of round or spindle cells, grow rapidly, and having once grown through the sclera, rapidly form metastases. They are seen as flat, sessile growths, lifting the retina as they progress.

Retina.—The only important tumor arising from the retina is the **glioma,** to which we have previously made reference. The tumor grows rapidly, filling the globe, making its way through it and appearing as a fungating luxuriant growth that spreads with great readiness. Its cells are small, closely packed, and with special stains the spider-leg processes can be demonstrated. It occurs invariably in infancy.

The Vitreous and the Aqueous.—In the foregoing consideration of the diseases of the eye, no mention has been made of the **vitreous** or the **aqueous.** The vitreous, it will be recalled, is not a fluid but a gelatinous substance which, if allowed to escape, is not replaced, which, too, may by injury become on the one hand **fibrillated** and on the other, **liquefied.** Should it become fibrillated, it is less transparent and may contract, pulling with it the delicate retina away from the choroid. By reason of its position and consistence, the vitreous is the medium into which exudate is thrown as a result of inflammation of the parts of the eye in contact with it. .

While making reference to the aqueous, the secreted fluid of the anterior chamber, seems the best occasion on which to deal with **glaucoma,** a very important disease which is characterized by increase of intraocular tension, with resultant pressure on the structures in the eyeball. Glaucoma may arise from inflammatory causes, in which case a few hours suffice for its development, or it may arise insidiously, and be discovered only when an ophthalmologist is consulted for failing vision, or when the patient discovers that one eye is blind. In such a case the damage is already done, but in the first-named form, treatment may be effectual. The name glaucoma is given because of the greenish reflex that is given from the pupil to the eye of the beholder; instead of a black color of the pupil, the beholder seems to see a green color; the eyeball is hard, tense, and the cornea dull; the aqueous humor, ordinarily drained away by the canal of Schlemm and the spaces of Fontana, fails to find escape, owing to blockage of these passages by narrowing or obliteration of the angle of the anterior chamber. Owing to the great intraocular pressure the optic disk becomes **cupped,**

which cupping, together with the hardness of the eyeball, is sufficient to allow recognition of the disease.

The Optic Nerve.—It is necessary to point out one at least of the pathological processes that affect the optic nerve. The most important is **choked disk,** the name applied to the papilla altered in certain pathological states, as when there is a more than normal intracranial tension, such as is produced by the presence of a new growth or an inflammation of the membranes of the brain. Some of the names applied to choked disk, such as papillitis and optic neuritis, imply that the change is an inflammatory one, but this is probably not the case, although the appearance of choked disk is seen as part of a papillitis or optic neuritis. Choked disk is an œdematous state of the optic papilla. As the optic nerve is continuous with the brain substance, the cerebrospinal fluid surrounds it in the optic nerve sheath, and may press upon it; thus the central vessels which come to run inside the nerve itself are likewise compressed and œdema of the papilla and the most distal part of the nerve results. In a moderate degree of choked disk, the outline of the papilla is blurred and indistinct, the papilla reddened and swollen, especially in its nasal half, while the retinal vessels are enlarged and tortuous. In more extreme cases, there may be splashes of hemorrhage on the disk. Should œdema persist, atrophy of the nerve fibres of the disk may be the result.

Neuritis of the nerve trunk may occur from an orbital or a meningeal infection. We have previously pointed out the liability of the nerve trunk to fibromatosis, and true **neuroma** has been found.

The Orbit.—The eyeball is suspended, as it were, in the bony orbit, and between the globe and the bone there is, therefore, a considerable bulk of muscles and connective tissues, not to mention fat and the vascular and nervous structures that are placed there. Inflammation of these soft tissues occurs, as a diffuse **cellulitis** or as **abscess,** resulting from trauma or infection; to the latter the orbital tissues are exposed, for infection may spread from the face, the cranial cavity, the bones, or the lacrimal gland and its subsidiary mechanism, the lacrimal duct.

Tumors of many orders are found in the orbit, apart from those that may spread from the globe: **angioma, osteoma, myoma,** and **teratoma** are found, while **sarcoma** is fairly common; **carcinoma** is only secondary, or by extension. Cysts of many sorts, including **hygroma** and others of like congenital origin, may be seen.

THE EAR

Abnormalities.—Anomalies of the different parts of the auditory apparatus are numerous, but relatively unimportant; considering the origin of these structures, those that affect the middle and internal ear are usually associated with other defects, such as harelip and cleft palate; the auricle may be abnormally small, abnormally large, or accessory auricles may exist. The external auditory canal may be

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absent, stenosed, unusually **narrow**, unusually **wide**, or even **duplicated**. The drum membrane may be **absent** or **fissured**. The middle ear may be **absent**, as may the Eustachian tube, or the latter may be **curved** abnormally or may open in an unusual place. The internal ear may be **absent** or abnormally developed, or may show lack of some of its parts, while even the auditory nerve has been known to be wanting.

Circulatory Disturbances.—*Auricle.*—The peculiar liability of the auricle to be damaged by freezing is well known. **Hyperemia** is usually a result of such thermic or of mechanical causes. **Hemorrhage** occurs—**hematoma auris**—as a result of trauma or without known cause, as is seen in the insane (possibly here also from unnoted trauma), in whom it may be bilaterally symmetrical.

External Auditory Meatus.—Circulatory changes are not of importance apart from the inflammations or traumas with which they are associated.

Drum Membrane.—**Hyperemia** may be observed as a distinct reddening of the part, the enlarged individual vessels being visible in states of inflammation. **Hemorrhage**, of punctiform nature, may occur in the membrane, and may show upon one or the other side.

Middle Ear.—**Hyperemia** occurs as part of the inflammatory process, and as the result of general passive congestion of the head region. **Hemorrhage** is usually the result of trauma or of a particularly virulent infection—**hemorrhagic otitis media.**

Internal Ear.—**Hyperemia** and **hemorrhage** occur under conditions similar to those in which they arise in the middle ear, but hemorrhage is of more importance, as it may cause deafness, and the absorption of even a moderate hemorrhage may be attended by damage to the delicate structures involved.

Inflammation.—*Auricle.*—Any of the inflammatory processes which affect the skin may affect the auricle. The inflammation which follows freezing is familiar, the auricle becoming swollen, bluish red, and painful; blisters may form on the surface, and even gangrene may follow. Inflammation of the perichondrium or of the cartilage itself may accompany this or other form of injury. **Perichondritis**, secondary to injury, as at operation or after hematoma, is occasionally followed by slight deformity of the pinna which appears wrinkled.

External Auditory Meatus.—Inflammation may be localized, as in the common **furuncle**, whose origin can be readily understood when it is considered that the wall of the meatus is exposed to contact with discharges from the middle ear, is liable to **eczema**, and does not readily lend itself to complete cleanliness. On the other hand, inflammation of the meatus may be diffuse, from the same causes, especially in patients whose resistance is poor; secretion tends to form upon the wall, which is shed off from time to time and as quickly renewed. The infection may be confined to the soft parts, may be superficial, or **periostitis** and implication of the bone may arise; in any of these cases an **abscess** may form. Membrane may form from **diphtherial** or other infection,

and **mycosis**, or infection by moulds, is seen. The **infective granulomas** affect the meatus, **tubercles** being found on the cartilage of the auricle or in the skin. **Syphilis** may show itself in ulceration or in inflammation of the cartilages; gumma is not unknown. Both of these infections are rare.

Drum Membrane.—Inflammation of the drum membrane or **myringitis** is usually the result of extension from nearby structures, especially the auditory canal. The membrane becomes red, swollen, soft, and even tiny abscesses may be seen; in cases where the inflammation persists the surface may become granular. The membrane has been seen affected in both tuberculosis and syphilis, in patients who have lesions of these diseases in the middle ear or other nearby structures.

Middle Ear.—Inflammation of the middle ear—**otitis media**—is a frequently found and important disease. Clinically, it is divided into well-defined groups, the acute and the chronic, while pathologically, one may recognize a simple, often catarrhal, and a suppurative form.

Trauma is often responsible in part for its origin; the infection, which is always present, may come from the Eustachian tube, which affords direct continuity to the infections of the pharynx, or through a damaged membrane, or by the blood or the lymph. There is no specific microbe, for many are effective in its causation.

In **acute otitis media** of a simple type, the mucous membrane of the cavity is reddened, congested, and swollen, with an abundant production of mucin in which appear degenerated cells and a few leukocytes; the submucous tissue is infiltrated with cells. The drum membrane shares in the inflammation, and **perforation** may occur. It is not easy to draw a sharp line of distinction between this and the suppurative form, into which, indeed, it frequently passes. In the latter, the secretion is frankly purulent, the inflammatory infiltration is greater, and there is a greater liability to ulceration and necrosis than before. In considering infective diseases of the middle ear, we must remember that the mastoid cells represent an extension of the antrum in the upper back part of the middle ear, and that these cells are probably involved to a greater or less extent in every acute process, although not necessarily to a degree which will be evident clinically. By reason of the smallness of the outlet from the cells to the middle ear, retention of secretion in the mastoid cells is apt to occur, which retention is largely responsible for the clinical signs of **mastoiditis**. Spontaneous cure of the disease, in fact, is to be looked for rather in the absorption of the exudate and the resolution of the inflammation than in actual drainage. Extension of the disease follows the failure of resolution or of drainage, and tends to involve the bone in the direction of least resistance, which may lead to extradural inflammation, **labyrinthitis,** or infection of the lateral sinus.

A persistent infection without the formation of pus may be the result of a simple acute infection; the changes are chiefly of hypertrophic nature. **Chronic suppurative otitis media** is, however, of much

greater importance, and should be considered under two heads. In the first of these the cause of the chronicity lies in the Eustachian tube and pharynx, and the middle ear is inflamed secondarily by the persistent discharge passing through it. This type is best illustrated by the group of cases which depend for their chronicity upon adenoid masses and enlarged tonsils. In the second group, the chronicity depends upon definite pathological changes in the middle ear especially in the attic, antrum, and mastoid, where the lining of the cavity and even the bone itself is attacked. Here belong the cases where the lining has become epidermized, either by metaplasia or by extension from the external auditory meatus, and the formation of **cholesteatoma** occurs. Cholesteatoma is an aggregated mass of desquamated epidermal cells and debris accumulating from the walls of the cavity which has become lined by new squamous epithelium. Such are the cases in which the discharge is purulent and foul smelling. It is especially in this group that danger of intracranial complication exists and the urgency of a given case depends largely upon the particular part attacked and the tendency to retention, since retention leads to bone destruction. It will be understood that in either of these groups the mucous membrane may be considerably hypertrophied even to the extent of polypoid excrescences, the ordinary **aural polyps.**

Chronic adhesive otitis media, which is the commonest cause of deafness, is known also as **sclerosing otitis,** and arises from the occurrence of adhesion between the ossicles and the walls of the cavity. Specially important is the involvement of the stapes in the oval window. These adhesions may be the result of a former suppurative otitis or may be of very slow formation from long-continued catarrhal processes in the middle ear. These cases are prone to begin in childhood, at which time the submucous tissues are normally more abundant than in adult life. With chronic inflammation this tissue is not absorbed and tends to become organized.

Otosclerosis is sometimes incorrectly called "dry catarrh." It is of unknown origin and depends on change in the labyrinth capsule with exostosis, especially liable to occur in the region of the oval window; it is important when it causes a bony ankylosis of the stapes in the oval window itself. Such foci of disease may occur in the cochlea, when an atypical clinical picture of nerve deafness is presented.

Tuberculosis occurs in the middle ear as a somewhat late manifestation of a severe infection elsewhere in the body. There is no special characteristic to be noted, save that the process is suppurative and attended by a rather rapid necrosis of the tissues.

Internal Ear.—Inflammation of the internal ear may be said to be always secondary, either to an infective process in the middle ear or within the cranial cavity. Extension commonly occurs from the middle ear by erosion of the bony wall at some point, or extension through the membranous closures. Secondary to a meningitis, the internal ear may be infected by extension from the internal auditory meatus or some of the

lymphatic connections. This involvement, secondary to cerebrospinal meningitis, is perhaps the commonest cause of **deaf-mutism**.

Regressive Changes.—*Auricle.*—The only regressive change that need be here mentioned is the occasional **calcification** of cartilage, and the **tophus**, a deposit of urates which is seen in gout.

Drum Membrane.—**Atrophy** of the membrane, with thinning and consequent increased transparency, is noted subsequent to chronic catarrhal states of the middle ear.

Internal Ear.—Sporadically and in some families there seems to be occasionally a special tendency to degeneration of the cells of the spiral ganglia, leading to deafness.

Progressive Changes.—*Auricle.*—These differ in no way from those occurring in the skin and subepidermal tissues elsewhere.

External Auditory Meatus.—Polypoid overgrowths of the mucosa are seen, the result of inflammation; **exostoses** of considerable size are found, sometimes pedunculated, often spherical. Various kinds of tumors may be found, such as **fibroma, lipoma, angioma, osteoma, sarcoma,** and **carcinoma; sebaceous cysts** are occasionally present.

Middle Ear.—Inflammatory overgrowths and tumors are found with fair frequency in the middle ear. As a result of inflammation, polypoid growths with connective-tissue core and epithelial covering, grow from the wall; such a growth is a potent factor in the continuance of any inflammatory process that may exist. **Fibroma, angioma,** and **adenoma** may be found. **Sarcoma** and **carcinoma** are rare and oftenest secondary.

CHAPTER X

THE DIGESTIVE SYSTEM

THE MOUTH

Abnormalities.—The most frequent and characteristic abnormalities encountered are harelip, cleft palate, defects in the number, arrangement, and growth of the teeth, and abnormal shortness of the frenum of the tongue (**tongue tie**).

Harelip and Cleft Palate.—It will be remembered that in the development of the face the intermaxillary processes of the first visceral arch project into the processus interglobulares and undergoing fusion in the middle line, are separated on either side by a cleft from the lateral frontal processes, which give rise to the lateral facial parts—this cleft running from the mouth to the orbit. Later by the development of the nasal passages, the upper portion of this cleft becomes divided into an orbital and a nasal portion. The former becomes closed at

a relatively early date, the latter remains open for a somewhat longer period as a cleft of communication between the roof of the mouth and the nasal passage of that side. Through arrested development we encounter, therefore, these various grades of malformation, either unilateral or bilateral.

1. **Cheilognathoprosoposchisis,** persistence of primary lateral facial cleft. This, the extreme condition, is rare.

2. **Median cleft of lip,** without development of the nasal passages, owing to lack of development of the intermaxillary (**arrhincephaly**), is very rare.

3. **Cheilognathopalatoschisis,** cleft of lip, jaw, and palate, unilateral.

4. **Cheilognathoschisis,** cleft of lip and jaw, bilateral, the intermaxillary forming an isolated median projection; rare.

5. **Cheiloschisis,** harelip. This is the slightest grade affecting what is the last portion of the cleft to undergo closure; is most often unilateral and on the left; the more pronounced form has associated (unilateral) cleft palate.

Defects of the Teeth.—Among these may be noted: lack of development of one or more wisdom teeth, irregular position of teeth, persistence of milk teeth with coincident presence of milk and permanent teeth. Lack of development of the jaws to the full size leads to abnormal closeness of the teeth. Some recent writers ascribe the increased irregularity of position and protrusion of the front teeth to the employment of infant "comforters"—dummy rubber teats sucked for hours at a time.

Hutchinson's teeth are characteristic upper central incisors of the primary set. They are stumpy, of peg shape, with a concavity of the cutting edge; they are frequently ridged and discolored. Hutchinson regarded them as a sign of congenital syphilis; while they occur in true congenital syphilis, it is debatable whether they are not also a parasyphilitic development (see p. 61). Nor are they wholly pathognomonic, being met with also in rickets.

Defects of the Tongue.—**Tongue tie** is not uncommon, leading to delayed speech; it is remediable by a simple surgical operation. A rare malformation of the tongue is **macroglossia,** or large size of the organ, brought about by congenital obstruction of the lymphatics.

Circulatory Disturbances.—While not infrequent and easily recognizable, these call for little special note, save as a reminder that the appearance of the lips and gums affords valuable indications of general **anemia** or **hyperemia.**

Inflammation.—According to the part specially affected we speak of **stomatitis** (inflammation of the mouth), **cheilitis** (of the lips), **gingivitis** (of the jaws), and **glossitis** (of the tongue). Considering how the mouth is exposed to infection and trauma it is remarkable to notice how relatively rare are serious inflammations of this region. In other words the protective mechanisms are here highly developed. Wounds of the mouth heal in general with extraordinary rapidity. This

does not mean that inflammations of various orders are not met with; on the contrary. Some of them, too, are characteristic and deserving of notice. More particularly it would seem that the mouth is markedly influenced by disturbances affecting the other portions of the digestive and respiratory tracts. Here may be mentioned the **herpes labialis** that frequently accompanies lobar pneumonia and other infections, and the catarrhal glossitis accompanying intestinal infection. As a class general infections exhibit an associated inflammation of the buccal mucosa, and the condition of the tongue and lips, varying as they may in the different infections, is employed as a valuable diagnostic aid. We would recall **Koplik's sign** in measles (the appearance of punctate hyperemic spots of pinhead size, often with a paler bluish centre on the mucosa of the cheeks and lips. These may be present hours or days before the development of the skin rash); the **strawberry tongue** of scarlet fever (due to intense congestion and swelling of the papillæ with loss of the epithelium over them); the catarrhal exudate upon the tongue, lips and gums of the typhoid patient, which, accompanied by extreme dryness of the mouth, leads to the production of **sordes**, dry, dirty-looking, superficial deposits. Cases are on record of a vesicular stomatitis resembling in its characters the highly infectious "foot and mouth disease" of cattle and brought about by drinking the milk of infected animals. In smallpox, chickenpox, and erysipelas, also, when the mouth is affected, a vesicular and later ulcerative eruption may be present.

Other characteristic forms of inflammation of the mouth are:

Thrush.—This is a form of spreading membranous stomatitis, beginning on the tongue and mucosa of the cheeks, found in infants and greatly debilitated adults, following, it would seem, the acid fermentation of milk and starchy foods, and caused by the superficial growth of a fungus, the *Oidium albicans*. Beginning on the surface of the epithelium the fungus may extend into the deeper structures.

Stomatitis.—**Aphthous stomatitis** is characterized by the formation of **aphthæ**, yellowish-white, thin plaques standing out against the reddened mucosa of the cheeks, lips, tongue and bases of the gums but not on the gums themselves. These seem to be of the nature of a fibrinous exudate. This condition is most common in poorly nourished children at teething and after acute and weakening diseases (bronchopneumonia, whooping cough, etc.), but also may occur in pregnant women and in men after exhausting disease.

Ulcerative stomatitis shows itself most characteristically in the jaws and around the teeth. The gums become œdematous and spongy, easily bleeding and breaking down. With this the teeth are apt to become loosened. The jaw bone may be exposed and undergo necrosis and the ulcerative process become very extensive. The condition is met with in scurvy, as also after poisoning with phosphorus, lead and copper. With phosphorus the liability to necrosis of the jaw bone is very pronounced.

Noma or **gangrenous stomatitis** is a very acute and fatal condition beginning usually on the cheek and rapidly spreading, with intense congestion and œdematous swelling of the affected parts, and rapid necrosis. With rare exceptions it affects poorly nourished and weakened children. The rapid gangrene is very striking and suggests some specific agent, but that there is such has not yet been determined. Several workers have encountered the Bacillus fusiformis with its accompanying spirochete. Others have encountered the diphtheria bacillus. **Suppurative stomatitis** with the development of abscesses, more particularly in the substance of the tongue, is comparatively rare.

Among the more chronic conditions are to be noted:

Leukoplakia.—Leukoplakia is a condition following chronic irritation, characterized by epithelial overgrowth and thickening and the formation of plaques of a whitish appearance on the tongue and mucous membrane of the cheeks. There is here superficial cornification of the thickened epithelium. This condition is seen in smokers, alcoholics and not infrequently in those affected with syphilis, and may be so extensive as to give rise to the **geographical tongue**, that is, a tongue divided into contrasted areas like countries upon the map of a continent. There is a distinct tendency in these cases to the formation of intractable fissures and slow ulceration, which may pass on to the development of epithelioma.

Syphilis.—Syphilitic lesions of the mouth are relatively common, more frequent than tuberculous. They may be (1) primary, the **chancre** appearing on the lips or on the tip of the tongue; (2) secondary, as an erythema, diffuse or in circumscribed patches leading more particularly on the lips to fissures and erosions. **Mucous plaques** may appear during the secondary stage or later in the disease. These may be present on the lips, cheeks, palate, and elsewhere. At first there is a warty or condylomatous thickening. This tends to break down, leaving shallow ulcers which heal with considerable scarring; (3) **gummas**, the characteristic tertiary manifestation. These show themselves in the substance of the tongue and on the gums.

Tuberculosis.—Tuberculosis of the mouth is rarely primary, and its seat is the tongue, and here most frequently laterally; along the edge, the tubercles tend to break down, leaving ulcers with thickened and swollen edges, not so hard to the feel as those of carcinomatous ulcers.

Actinomycosis.—Actinomycosis in man, from our experience, starts most frequently in the cheek, though cases are found in which, as in cattle, the growths begin in the gums and extend into the bone. **Leprous nodules** may show themselves beneath the mucosa of the mouth.

The three chronic conditions most liable to be confused in connection with the mouth, and more particularly the tongue, are tuberculous ulcers, syphilitic ulcers and epithelioma.

Progressive Changes.—We have already referred to leukoplakia, a condition of overgrowth and thickening of the squamous epithelium covering the tongue. Of the tumors proper, the connective-tissue

group (fibroma, lipoma, myxoma) is occasionally encountered. The term epulis is employed for rounded tumors of benign type projecting from the gums. The term thus includes fibroma and giant-celled myeloma (or sarcoma). Rarely do these take on very malignant properties. The mouth is lined by squamous epithelium, and thus the typical epithelial tumor from this region is the epithelioma, or squamous celled cancer (p. 386). Such epithelioma may affect the lips and the tongue, more rarely the gums. The characteristics of these epithelial tumors are the formation of well-marked cell nests, with extensive superficial ulceration and the relatively rapid involvement of the lymph nodes at the base of the tongue and in the neck.

Epithelioma may also arise from the upper portion of the pharynx and occasionally from the lower portion above the laryngeal opening, in which case the epithelial origin is from the sinus pyriformis. This form is difficult to distinguish from primary cancer of the larynx. Kaufmann lays down that while laryngeal cancer is for long unaccompanied by any secondary growths in the cervical lymph nodes, pharyngeal cancer is apt to be accompanied by a relatively enormous infiltration of these nodes.

Teratomas are occasionally encountered growing from the pharynx (epignathus, p. 817), or from the palate. Occasionally within the tongue substance posteriorly may be cysts developed from the primitive thyroglossal duct or from an aberrant process of the same, the so-called "Bochdalek's glands." These cysts may be lined by a ciliated epithelium. Other cysts may occur in the ducts of the salivary and mucous glands through obstruction and retention of their secretion. The so-called ranula occurs in the neighborhood of the frenulum, and is said to be due to a dilatation of the duct of one of the Blandin-Nuhn mucous glands in this neighborhood.

Nearly every form of benign tumor has been occasionally described in connection with the soft palate, pharynx, and tonsils; fibromas, chondromas, lipomas, angiomas, and, as already noted, teratomas (epignathus, p. 817). The most common growth is the nasopharyngeal polyp, and most often appearing in children. These tumors are of the same order as the nasal polyps already described. It is worthy of note that the latter may frequently project into the upper pharynx. Of the malignant tumors, large and round-celled sarcoma of the tonsils and pharynx are occasionally encountered. Epithelioma may also originate over the tonsils, and is peculiarly apt to lead to extensive ulceration, with erosion, and liable to cause death from involvement of the carotid. It is distinguishable from a chancre of the same region by its undermined edges and more nodular floor.

As might be expected from the abundance of lymphoid tissue in the pharynx, the various orders of lymphosarcomatous growth are encountered in this region. Thus in leukemia there may be overgrowth of both the tonsils and the general submucous tissue of the pharynx. Very similar overgrowth may be encountered in the preleukemic or

aleukemic conditions, while, further, **lymphosarcoma** may show itself primarily in the tonsils, and then is apt to be rapidly infiltrating. Such growths are very vascular, easily break down, and lead to gangrene and hemorrhage.

THE TEETH

A few words should here be given regarding diseased conditions of the teeth which the ordinary medical man is apt to neglect, although we are coming to realize that they are of material influence upon the general health.

Caries.—Caries is the commonest of these disturbances. The process is due to a progressive decalcification and destruction of the substance of the tooth. It is brought about by the agency of microorganisms which, producing acids, dissolve out the calcium salts. These bacteria gain entrance through erosions of the enamel and grow along the canals of the dentine. While this is the case, it has to be recognized that the tooth is not wholly inert matter, and that its power of resistance to this microbic invasion varies greatly. French writers, more particularly of late, have called attention to the fact that during pregnancy, and in the early stage of tuberculosis, there is a distinct lowering of the general calcium content of the organism and coincidently a marked liability for the rapid supervention of dental caries.

Pulpitis.—Simple caries is unassociated with pain, but where it is present microörganisms have penetrated along the dentine canals to the pulp and there set up an acute inflammation that is intensely painful. The exudate may be of suppurative type and so form an abscess, destroying the pulp and extending to the root of the tooth and so to the alveolus, inducing an alveolar periostitis; or again the pulp cavity remaining closed, the abscess may make its way (1) through the bone of either jaw, usually on the outer aspect, and here either discharge itself or undergo absorption; or (2) abscess of the upper jaw, notably of the canine teeth, may extend upward and set up acute inflammation of the antrum of Highmore.

Pyorrhea Alveolaris.—This is a form of low suppurative alveolar periostitis, originating, it would seem, not from the root of the tooth, but at the angle between the gums and the teeth and gradually working downward, loosening and leading to the falling out of tooth after tooth. The condition is in general painless, and apt to escape notice, save on examination. This condition has come in for increased recognition of late years owing to the teaching of Hunter and others. It is held that the constant discharge of the infected pus and the swallowing of the same leads to a low and continued form of gastric inflammation which, in its turn, is responsible for the supervention of grave anemia. To suppurative conditions in association with the teeth have also been ascribed the occasional development of aspiration pneumonia, gangrene of the lungs, and chronic swelling of the lymph nodes in children.

Such pyorrhea is said to be often preceded by **tartar of the teeth**. This is a very common affection and easily set up if the mouth be not washed out after meals. Portions of food, cell debris, etc., collecting in the angle between the tooth and the gum become the seat of growth of leptothrix and other bacterial forms, and, as noted on page 282, calcareous salts are apt to be deposited in the broken-down material so that a calcified layer of extraneous matter coats the lower part of the tooth. If left, as the epithelial scales are given off from the surface of the gum and are prevented from being swept away by the calcified matter above, these dead cells in their turn become the seat of a calcareous deposit, and so the tartar appears gradually to push its way downward separating the tooth from the gum.

Tumors of the Teeth.—The development of the tooth as a differentiated portion of the epithelium of the jaw is a complicated process, and hence quite a series of tumors may develop from one or another portion. These tumors may be either solid or cystic. Of the former, there may be localized overgrowth of the enamel, **adamantinoma**, excessive localized development of the dentine, **odontoma**, of the cement substance, **dental hyperostoses**, while from the root of the tooth there may be either connective tissue or epithelial growths. Kaufmann divides the cystic overgrowths which may be found in the jaw as follows:

    a. Tooth cysts.
    b. Root cysts.
        (1) Simple.
        (2) The periosteal cysts of the jaw.
    c. Multilocular cystomas.

The simple tooth **cysts** originate from normal or accessory tooth germs or misplaced portions of such germs. These cysts, lined by an epithelium, are most often unilocular, but may be multilocular, and they may contain rudiments of teeth.

Root cysts are the result of periostitis of the root.

The multilocular cysts are thin walled, causing absorption of the bone of the jaw with great swelling of the same.

SALIVARY GLANDS

Inflammation. — The most important condition in association with the salivary glands is **angina ludovici** (Ludwig's). This is a very acute inflammation of the floor of the mouth and of the upper portion of the neck, which is supposed by many authorities to originate from the submaxillary gland. It is a rapidly extending infiltration, the surrounding tissues tending to suppuration and gangrene, and it is liable to end in a general bacteriemia or fatal œdema of the glottis.

Mumps or epidemic parotitis is a highly infectious condition characterized by pronounced enlargement of one or both parotid glands and

accompanied by a moderate grade of fever and general disturbance. That the infection is not merely local and confined to the parotid is shown by the frequent coincident **orchitis** in the male and by an inflammation of the ovaries or mammæ in the female. The disease more particularly affects the male sex before the age of twenty, and the left parotid is apt to be more involved than the right. Bilateral painless swelling of the parotid (and lacrimal) glands has been described under the name of **Mikulicz's disease**, and most cases are probably inflammatory in origin, although some are allied with leukemia.

Tuberculosis and other specific inflammations of the salivary glands are relatively rare. Concrements (**sialoliths**) forming in the ducts of the salivary glands are occasionally encountered. These result from catarrh with obstruction.

Progressive Changes.—Tumors, more particularly of the parotid, form a complicated series of growths, nor can it be said that the exact relationship of the series has been fully established. Occasionally we encounter pure adenomas and pure adenocarcinomas; more frequently there is an admixture of cell groups of very different types, what appear to be epithelial elements intermixed with fibrous, cartilaginous, or more actively sarcomatous developments. As a rule, these mixed tumors grow slowly, and while they are apt to spread locally, despite their malignant appearance they show little tendency to recur after removal. More particularly these tumors are apt to show cells of the connective-tissue type, or sarcomatous, in definite relationship to the vessels of the part, the so-called perivascular **endotheliomas** or **peritheliomas**, or where the outer masses of cells undergo hyaline degeneration (**cylindromas**). It is often difficult to come to a determination whether the alveolar masses of cells of these mixed tumors are of epithelial or endothelial origin. We are inclined to state that no satisfactory or generally accepted explanation has been afforded for the frequency of these mixed growths of this particular region. Tumors of the same order, though rare, have been described in association with the submaxillary gland.

THE ŒSOPHAGUS

Notwithstanding its exposed condition—its liability to infection from food substances and discharges swallowed from the mouth, its liability also to traumatism from the food, affections of this organ are relatively uncommon. In other words the lining squamous epithelium is endowed with considerable resisting powers. When it is involved in disease the effects upon nutrition are very serious, hence such disorders of the œsophagus as show themselves are of very considerable clinical importance.

Here certain anatomical data may be recalled. Averaging 25 cm. or 10 inches in length in the adult, the œsophageal tube is pressed upon a little below its origin by the cricoid cartilage, then 8 cm. below its

origin by the left bronchus which crosses it, and shortly before its
termination in the stomach it passes through and is apt to be compressed
by the diaphragm. It is at these points of relative narrowing that
irritant matter taken with the food is apt to suffer relative arrest and
these, therefore, are the sites of election for morbid states. In the
upper portion the muscle is striated, in its lower plain and involuntary.
As throughout the digestive tract, this muscle is arranged in an outer
longitudinal and inner circular layer. There is also a well-developed
muscularis mucosæ. The mucosa is formed of a squamous epithelium
with occasional mucous glands. In some 15 per cent. of normal indi-
viduals small islands of cylindrical-celled epithelium are encountered
in the upper half of the œsophagus. On section, these closely resemble
the gastric mucosa, and have been regarded as such by some authorities.
Schridde has pointed out, however, that the originally cylinder-celled
epithelium of the foregut gives rise to various orders of epithelium,
and that in these islands it has proceeded to develop into a cylinder-
celled modification rather than into a squamous-celled; these are not
gastric cell-rests in the proper sense of the term.

Malformations.—These are uncommon. There may be complete
absence (agenesia) or in part the tube may be represented by a fibrous
cord, the organ thus forming a blind sac. Occasionally there is
communication with the trachea. Partial or complete **duplication** has
been recorded, localized narrowing or **stenosis**, and the presence of a
fold or diaphragm, causing **occlusion**. It must be remembered that
the respiratory system originates as a diverticulum from the primitive
foregut, and occasionally we encounter cysts in the upper thorax
lying between the œsophagus and the trachea, lined by ciliated epithe-
lium; or we find isolated accessory masses of lung tissue immediately
above the diaphragm. These must be regarded as originating from
accessory respiratory diverticula.

Acquired Malformations.—Occasionally in hysterical individuals and
nervous states contracture of a portion of the œsophagus is brought
about by muscular spasm. Whether from such continued spasm, or
from acquired stenosis (by pressure from without, by new growth in
the wall, or by cicatricial contraction after an inflammatory process),
the portion above the site of narrowing undergoes dilatation. This
dilatation is sometimes enormous. Idiopathic dilatation has also been
observed. A similar condition has been produced experimentally in the
dog after cutting both cervical vagi.

In addition to this generalized dilatation we recognize also local
dilatations or **diverticula**. These are of two orders, the so-called
pressure and **traction** diverticula. The latter are not uncommon, their
usual site being on the anterior wall just below the bifurcation of the
trachea. They are clearly associated with tuberculosis and other
inflammatory disturbances of the group of lymph nodes situated in the
angle between the two bronchi. As a result of this inflammation the
tissue around the nodes is involved and fibrous bands or adhesions

are developed between the nodes and the œsophageal wall. As a result with each peristaltic act, in swallowing, the œsophagus is pulled upon at this point and gradually a small expansion or saccule becomes developed.

The pressure diverticula are rarer. These occur at or in the neighborhood of the middle line on the posterior aspect of the œsophagus close to its origin. At this point the muscle wall is at its weakest. The usual teaching is that through the pressure of a large bolus of food the mucous coat becomes pressed outward through a defect in the muscle wall and soon a small amount of the ingested food or fluid collects in the lower portion of such an expansion, so that with the successive acts of swallowing the diverticulum gives way more and more; more and more foodstuff collects in the lower portion of the saccule thus formed, until gradually from the weight of this food and the irritation and weakening of the wall of the sac produced by the same, there is developed an elongated, blind sac, extending downward on one or other side in front of the vertebral column, it may be for several inches and even into the thorax. Usually no muscle fibres are found in the walls of this sac.

A perforating ulcer of the œsophagus, which has probably by irritation caused a spasmodic stricture of the cardia, this in turn producing hypertrophy of the œsophageal wall and dilatation of its lumen. Marked pyloric stenosis, of which the cause was not apparent. (Winkler.)

In this connection we may note certain other acquired conditions. **Rupture** is rare. **Perforation** may occur from swallowed bone, etc., from erosion, from syphilitic and cancerous ulcers, at the base of traction diverticula, by pressure of retained foreign bodies, or by extension of inflammatory conditions from without (caseous tuberculous glands, aneurysm, etc.).

Post mortem softening and rupture may be brought about by the action of the acid gastric juice. This may occur where there is relatively sudden death, with full digestion. Very rarely may this digestion occur *intra vitam,* with the production of ulcers at the lower end of the œsophagus of the same order as the peptic ulcers to be described later.

Circulatory Disturbances.—Of these the most noteworthy are the greatly distended varicose submucous veins of the lower extremity of the organ, seen in conditions of obstruction of the portal circulation, and, especially, in cases of portal cirrhosis of the liver. They are due to the development of collateral circulation through these veins between the portal system and the vena azygos. These lie so immediately beneath the surface that mere passage of food may lead to their rupture and fatal **hemorrhage**. In elderly individuals slight varices are not infrequent at the upper end of the œsophagus.

Inflammation.—In cases of general infection the œsophagus is rarely found involved. For example, while there may be an intense and extensive pharyngeal **diphtheria** extending down the respiratory passages it is very rarely that the œsophagus also shows a false membrane. It is rare also to find this organ the seat of either **tuberculosis** or **syphilis**. On the other hand, extensive inflammation may be set up from irritating food and by the accidental or purposeful swallowing of very hot water, lye, acids, etc. These may lead in the milder cases to an acute desquamative catarrh; in severer cases to necrosis and ulceration of the epithelium, more particularly at the regions of narrowing already noted. After such alteration, with cicatrization there may develop stenosis of the tube, with all its consequences. We have repeatedly confirmed the observation of our late colleague, Prof. Wyatt Johnston, that the condition of **leukoplakia**—streaks or patches of epithelial thickening and hypertrophy—is commonly to be met with in chronic drunkards. Here it would seem that we deal with a chronic inflammation of low grade, leading to epithelial proliferation. Other conditions of chronic catarrh, as for example, that associated with chronic passive congestion, may also be a cause of this condition.

Progressive Changes.—**Tumors.**—Benign tumors, **mucoid polyps, myomas,** and **lipomas** are relatively uncommon; so also are **sarcomas**.

The one frequent tumor is **primary carcinoma**. This in the majority of cases is of the nature of **epithelioma**, originating from the squamous epithelium of the organ. Occasionally we encounter medullary adenocarcinoma originating either from the mucous glands, or, it may be, from the above-mentioned islands of cylindrical epithelium. There are three main sites at which such a tumor may develop, namely, one of the three points of narrowing already noted. The statistics from different regions vary regarding the frequency with which one or other region is involved. Our own experience favors the middle region as the most common site, but many state that the diaphragmatic narrowing is most affected. The slower growing forms do not project extensively into the lumen but are apt to encircle it and become scirrhous, thereby inducing stenosis and obstruction. With the passage of food they are liable to break down in their central zone, forming thus a flattened ulcer with thickened raised wall, the tumor infiltrating beneath the mucosa and extending also into the deeper layers of the tube, so that with progressive ulceration there may be rupture into the medi-

astinum or thoracic cavity. Through infiltration upward and downward the growth may extend a considerable distance. Softer adenocarcinomatous growths, on the other hand, form large masses projecting into and blocking the œsophagus. The bronchial nodes are especially liable to be the seat of secondary growths; metastases at a distance are relatively uncommon. By direct infiltration the trachea, lungs or vertebræ may be involved. It will be understood that through the passage of food over the ulcerating surface, gangrenous conditions extending into the neighborhood are liable to supervene.

THE STOMACH

The stomach is of the nature of a pronounced dilatation in the course of the alimentary tube. This tube in early fœtal stages has a comparatively direct course in front of the future vertebral column, but, with further growth, that portion which is to be the stomach both increases in length so as to form a loop downward with what is to be the pyloric end remaining relatively fixed, and at the same time undergoes distension and some rotation, so that what had been the posterior aspect comes to correspond with the greater curvature turning to the left and forward. The wall consists of three main layers. From either side of the vertebral column the peritoneum passes to it to form a mesentery, whose two layers separate to cover it and join again along the lower aspect, now forming the great omentum, which passes down and returns to the vertebral column, whence again it is reflected over the transverse colon.

Beneath the serous coat is a loose connective subserosa. The muscle layers are well developed, consisting of an outer longitudinal, an intermediate, somewhat ill-defined oblique layer, originating from the former, and a circular layer. At the distal end of the stomach the musculature undergoes a marked increase so as to form a sphincter, the pyloric ring. The mucosa is relatively very thick, consisting of a cylindrical-celled epithelium with abundant long, glandular invaginations. These glands form simple and often in the pyloric portion forked tubules, differing in their constitution in the cardiac and the pyloric regions respectively. The cardiac region may present two orders of cells, namely, the more regular cylindrical chief cells, giving origin to a pepsin-containing secretion, and the angular or polygonal oxyntic cells, with a more peripheral position, giving origin to the acid of the gastric juice. These latter cells are wanting in the pyloric portion of the stomach.

Between the various gland tubules and again between the mucosa and the muscle layer is a well-defined submucosa, abundantly vascular, with occasional solitary lymph nodules. In the resting or contracted state of the stomach the mucosa exhibits a series of longitudinal folds or rugæ.

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As demonstrated by the usual method of fluoroscopic examination, after giving food mixed with bismuth the stomach physiologically consists of two distinct parts: first, after a meal the cardiac half is distended, the pyloric contracted, and only as the food becomes disintegrated through the acid cardiac secretion does constriction of the organ at its centre slowly give way, permitting the food to pass into the pyloric half, the cardiac portion now contracting. Following upon this the pyloric ring opens, permitting the softened food to pass into the duodenum.

Abnormalities.—Cases are on record in which the organ in the adult has been so small as to contain little more than an eggcupful of fluid, and others of entire **absence**. More common is abnormality of position with some persistence of the vertical relationship of fœtal life, although it is to be noted that fluoroscopic examination has shown us that the stomach is normally more vertical than was supposed, as well as lower in the abdominal cavity, at least, when it contains fluid or solids of weight. The most important abnormalities are congenital hourglass constriction and pyloric stenosis. Care must be taken to distinguish between three orders of **hourglass stomach**: (1) as demonstrated by Cannon's bismuth experiment, during the course of normal digestion there is a stage in which the cardiac is cut off from the pyloric portion by contraction of the middle zone of muscle and at times we find the stomach in this phase at autopsy. This physiological hourglass state can be reduced by distending and kneading the organ; (2) occasionally there is a state of congenital hypertrophy of the mid zone of muscle, the true congenital hourglass state, and lastly (3) the cicatrization and contraction of an old ulcer of the lesser curvature, which constricts the mid area, causes an identical appearance. The state of **pyloric stenosis** may similarly be either of congenital or acquired origin. The former manifests itself in infancy with symptoms of gastric obstruction, dilatation of the stomach, vomiting, etc., and on operation or at autopsy the obstruction is found due to extensive hypertrophy and contracture of the pyloric ring. The latter is often not a true muscular hypertrophy, but a fibrous overgrowth: in two cases we have found it to be of the nature of scirrhous cancer with abundant dense stroma and rare atrophied cancer cells.

Circulatory Disturbances.—Anemia is most often a part of general anemia of gradual production or from rapid loss of blood. Active **hyperemia** follows the reception of irritants into the stomach and is well seen in the early stages of acute gastritis.

Passive hyperemia is relatively frequent, manifesting itself in all cases of obstructive liver disease, and to a less extreme extent, though still markedly, in obstructive heart disease. In the former case, noticeably in cirrhosis, the congestion is associated with the development of a collateral circulation through anastomoses with the œsophageal veins. This persistent venous congestion favors the development of a chronic type of gastritis.

Hemorrhages are not infrequent. They may be either (1) minute, multiple, and in the main submucous, or (2) minute and free, constituting the condition of diffuse hemorrhagic oozing, from vessels so small as to be invisible to the eye; or (3) solitary, gross and free, leading to great sudden loss of blood and tending to grave results. Minute hemorrhages, ecchymoses, are seen in many different conditions: (a) in hemophilia, passive congestion, acute catarrhal gastritis, where there has been severe vomiting, phosphorus and arsenic poisoning, conditions, that is, associated with dilated or degenerated states of the capillary, or (b) they may be the result of a nervous or neurotic dilatation of capillaries as in hysteria and (probably) the gastric hemorrhages of pregnancy, or (c) they may follow the erosive action of caustic substances that have gained entrance in the stomach or (d) they may be secondary to multiple emboli in the gastric arterioles, or thrombosis of the larger gastric veins. The beginner must be careful not to confuse with these the common condition of apparent hemorrhage along the gastric vessels brought about by post mortem digestion, and due to diffusion of hemoglobin and changes occurring in the same.

The **submucous hemorrhage** is apt to induce necrosis of the immediately overlying mucosa by cutting off its nutrition. While the gastric juice can exert no influence upon the living cells of the mucosa, dead mucosa is acted on by it; there is in fact no difference between it and the dead animal matter that may be introduced into the stomach as food. It follows, therefore, that the state of multiple hemorrhages tends to give place to that of multiple **hemorrhagic erosions.** We shall describe these more fully under the regressive changes. We would suggest tentatively that whether there be developed easily recognizable submucous hemorrhages with little evidence of erosion, or on the other hand diffuse oozing with little or no indication of submucous hemorrhage is probably determined by the acidity and activity of the gastric juice. When this is powerful, so soon as a small area of the mucosa is of depressed vitality through underlying vascular disturbance, it becomes digested and removed, affording a minute ulcer with a bleeding capillary at its base.

Gross hemorrhages may be brought about by the rupture of a relatively large vein in passive congestion (most often in cirrhosis the rupture affects not the gastric but the lower œsophageal veins). Commoner causes are round ulcer and carcinoma. The very nature of the cancerous growth determines that where it infiltrates the surface the outermost layers are apt to be poorly nourished, to undergo necrosis and ulceration. The digestion, therefore, of the necrosed matter is apt to expose some deep vessel, weaken its wall and favor hemorrhage. In the peptic ulcer there is a similar process of necrosis, ulceration, and exposure of a deep vessel.

Blood discharged into the stomach and mixed with gastric juice takes on rapidly a brownish coffee-ground appearance owing to the action of the acid upon its hemoglobin.

Embolism and **thrombosis**, as already indicated, may involve the gastric vessels; we shall take up their effects in discussing the peptic ulcer.

Inflammation.—Acute Gastritis.—The historical studies of Beaumont on the stomach of Alexis St. Martin have taught us how easily errors of diet induce inflammatory changes in the gastric mucosa, an overdose of alcohol bringing about acute hyperemia and even the development of a vesicular eruption, with discharge of greatly increased amount of mucus. Acute catarrhal gastritis is characterized more particularly by this pouring out of abundant mucus from the goblet cells, along with other modifications in the composition of the gastric juice, notably diminution of the hydrochloric acid. The mucous membrane is hyperemic and may show ecchymoses. Histologically, in addition to the catarrhal inflammation of the mucosa, there is a small-celled infiltration of the submucosa with marked congestion.

Phlegmonous Gastritis.—This is a rare and fatal condition characterized by the formation of submucous abscesses which, spreading, separate the mucosa from the underlying tissues. With its necrosis the pus is discharged into the stomach and ragged ulcers develop, although it is surprising how much pus may lie in the substance of the stomach-wall without breaking through. In most cases the condition is of streptococcal origin and is one manifestation of the pyemic state; in others it is idiopathic, unassociated with abscess formation elsewhere. Drunkards show some predisposition to this form, presumably as a complication of subacute gastritis.

Membranous Gastritis.—Membranous gastritis is also rare, apt to be encountered more particularly in the newborn and young children, in whom, indeed, true gastric diphtheria has been recorded.

Follicular Gastritis.—As rare or rarer is follicular gastritis with pronounced enlargement of the small lymph follicles usually present in the submucosa.

Chronic Gastritis.—Chronic gastritis may be broadly of two forms: (1) hypertrophic and (2) atrophic. The first of these is seen more particularly in alcoholics and those suffering from chronic heart and liver diseases, although it may result also from any chronic irritation of the stomach, as from dyspepsia and prolonged retention of food in the stomach with delayed and perverted digestion. The mucosa is recognizably thicker than usual, of darker color, with at times some pigmentation, the result of imperfectly absorbed hemorrhages. There is increased mucous production and discharge, but what is most characteristic of the condition is the coarsely granular appearance of the surface, when the mucus has been washed off or otherwise removed.

Under the microscope there is found a distinct thickening of the submucosa with congestion and cellular infiltration; the infiltration and increased fibrosis extend between the gland tubules, which are further apart than in the normal organ. The mucosa itself in this form is well preserved and the coarsely granular appearance is due to closely packed areas of slight overgrowth, both of gland tissue and stroma.

These more typical cases give place to others in which the mucous and submucous hypertrophy takes on a papillomatous form, **gastritis polyposa**. Whether this polyposis is always the outcome of chronic irritation is questionable, but in some cases in which it is found there is definite history of such, in others the polypoid masses appear to originate from the edges of healed ulcers. It is possible that a proportion of cases represent a blastomatoid condition—a tendency, that is, to diffuse papillomatous overgrowth upon minimal irritation.

Atrophic gastritis may be the outcome of a fibroid hypertrophic gastritis; the atrophy of the glandular elements, that is, may be due to arrest of nourishment by the underlying overgrowth of connective tissue. In a considerable proportion of cases there is no very pronounced submucous fibrosis, but both mucosa and submucosa are diminished. It may, indeed, be questioned whether they would not be better placed among the regressive disorders than among the inflammations. Microscopically the gastric glands are greatly shortened with large lumen and cells relatively shrunken. The condition is not infrequently found associated with pernicious anemia and marantic conditions.

Specific Infections.—Of the specific infections **tuberculosis** is rare and never primary. **Syphilis** is also rare though ulcerations are occasionally observed, and the marasmus of the syphilitic child has been ascribed in part to the existence of subacute or chronic gastritis. Gastric **actinomycosis** and **glanders** have been recorded. Ulceration of the rare solitary lymph follicles of the stomach is one of the curiosities of **typhoid fever**.

Regressive Changes.—Of degeneration proper there is little that calls for further note, save that **calcareous deposits** have been described as occurring in the mucosa. Of greatest interest is the series of necrotic changes that may involve the mucosa and the various ulcerative processes from simple hemorrhagic erosions to the perforated peptic ulcer.

In speaking of phlegmonous gastritis we have already indicated that there may be ulceration of inflammatory origin in the stomach; the most common ulcers encountered in this organ are non-inflammatory. They are clean cut and upon microscopic examination the edges show little evidence of congestion and little or no small-celled infiltration. They are **peptic ulcers** due to the digestion and removal of an area that has become necrotic, and of these we recognize two main orders: (1) the multiple small and (2) the solitary or few large, the latter constituting the **round ulcer**. The ordinary text-book takes little note of the former, but we have encountered no less than six examples in the course of 1500 autopsies together with others that appear to be the early stage of the development. In this form there are found from fifteen to fifty or more small areas of loss of tissue of irregular shape and from 1 to 5 mm. across, most often in the middle zone of the organ, but at times more in the cardiac, at others more in the pyloric region. They have pale, clean-cut edges and in general a smooth base formed

of the submucosa or at most the muscularis. Their abundance and small size give the lining of the organ a decidedly moth-eaten appearance. Very rarely do they perforate. In none of the cases can we recall that there were any symptoms calling attention to stomach ulceration; no hematemesis, no melena. They have been associated with typhoid, peritonitis, and operation for the same, portal thrombosis and in one case with pyemia, in two with multiple infarcts in the kidneys, spleen, etc. One group of these cases is associated with submucous hemorrhages and belongs to the order of hemorrhagic erosions, for we have in our collection intermediate cases showing abundant small, submucous hemorrhages and intermingled with them numerous early ulcers of this type. The mucosa over the hemorrhages has undergone necrosis and digestion, and ulcer formation has been the result. Another group shows no sign of hemorrhage, and the presence of emboli elsewhere suggests that here the condition is due to multiple minute emboli of the branches of the coronary artery. In one case the ulcers occurred along the course of the branches of a thrombosed coronary vein. We must admit, therefore, that anything which causes local death of small areas of the mucosa becomes a cause of these conditions provided that the gastric juice retains its activity. Recently our colleagues, Drs. Rhea and von Eberts, have demonstrated in one case of widespread capillary oozing from the stomach wall that there existed multiple microscopic ulcers, the loss of tissue on the surface being very much less than in the underlying mucosa and submucosa.

Round Ulcer.—The more familiar round ulcer has the following characteristics: it is strikingly clean cut, when small (2 to 3 cm. across) it is round, when large it may be of irregular shape; it is often solitary, but there may be two or three present; it is sharply punched out and when small, is, if we may so express it, of a terraced, funnel shape, more of the mucosa being involved than of the submucosa, of the submucosa than of the muscularis (if it penetrate thus far). Its extent corresponds, that is, with the area of distribution of one of the gastric arterioles. Its walls show no signs of inflammation in the early stages; later with repair and the process of cicatrization these may be present.

One of two dangerous complications is apt to attend the development of this form: (1) **hemorrhage,** often fatal, from digestion of the artery of supply of the necrosed area down to the region where this has become occluded and (2) **perforation,** with escape of the gastric contents and supervention of peritonitis. Many of the ulcers fail to perforate freely, owing to the fact that with thinning of the stomach wall, adhesive inflammation is apt to be set up between the base of the ulcer and the pancreas, liver, or other neighboring viscus. In this case the digestion and perforation may extend some little way into the adherent organ. Free perforation is most apt to occur when the ulcer is situated on the front wall under the left lobe of the liver near the pylorus.

Etiology of Round Ulcer.—As to the cause of this form of ulcer there has been abundant hypothesis, nor is the matter by any means settled.

The anatomy of the ulcer indicates very strongly that it corresponds to an infarctous area caused by occlusion of a branch of one of the gastric arteries. An embolic cause is held by some and is supported by the results of experimental embolism, but the condition occurs most

Fig. 296
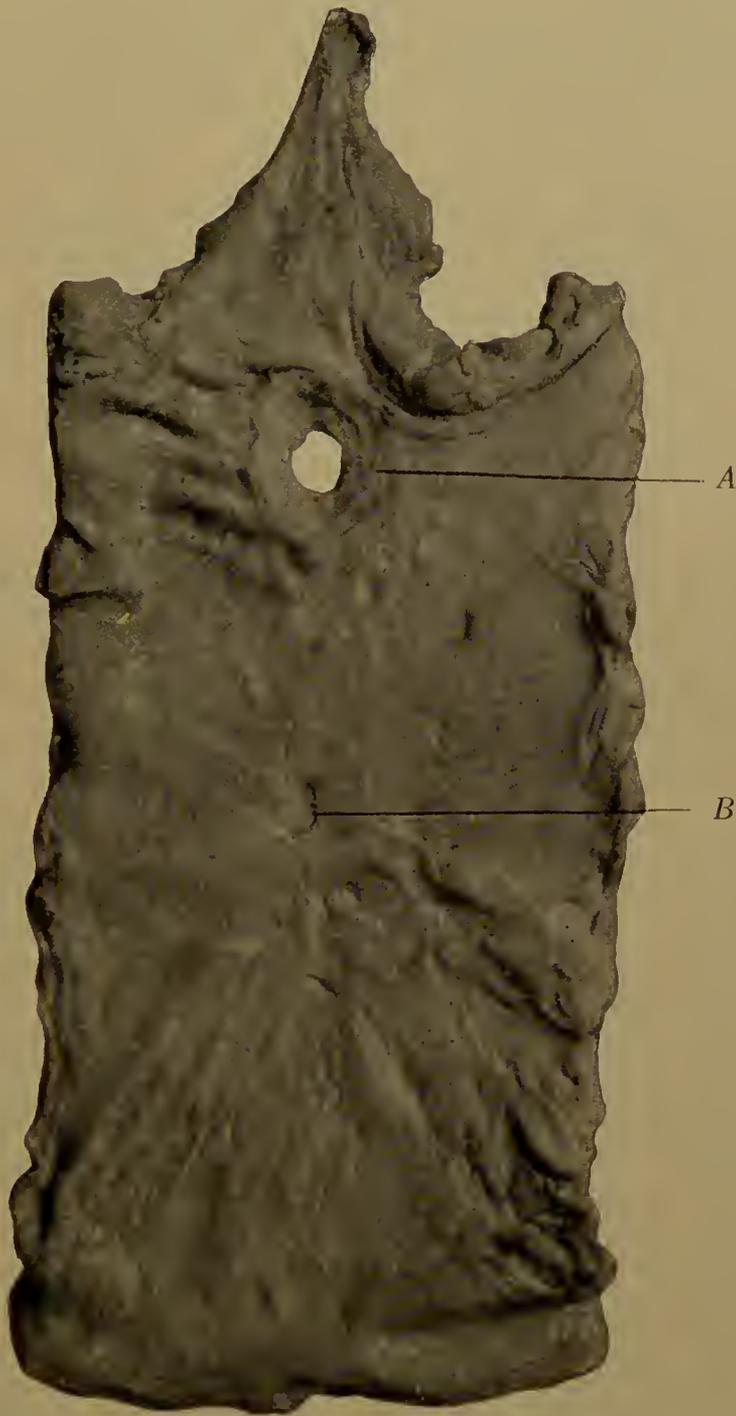
Stomach showing perforated, shelving gastric ulcer (*A*) and multiple scars of healed ulcers (*B*).
(McGill Pathological Museum.)

often in individuals, man and woman, who show no signs of embolism elsewhere. For this reason others have suggested a local spastic contraction of individual arteries, and yet others, seeing that the condition is specially frequent in the mid zone of the stomach, occlusion of a

branch of the coronary artery by the long-continued contraction of the muscularis which occurs after meals. The solitary nature of these ulcers is opposed to causation by irritants—hot foods, etc.—acting from within the stomach; such should set up multiple lesions. Nevertheless Turck has produced lesions of this type by repeated feeding with toxins of B. coli. Reford has regularly produced the like order of ulcers in the first part of the duodenum by ligaturing the common bile duct. Such ligature does away largely with the "alkaline tide" in this region and

Fig. 297
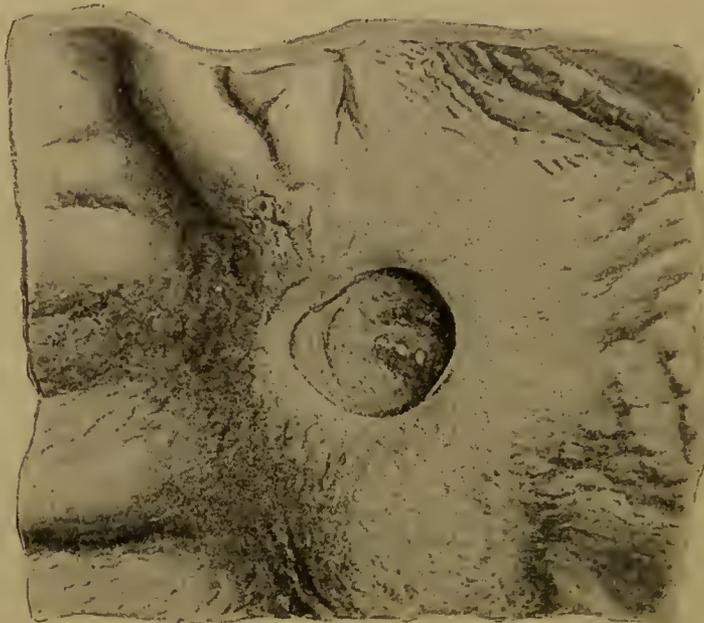
Round ulcer of stomach. (Stromeyer.)

favors thus the deleterious effects of the acidity of the chyme. Now it is to be noted that there is a close association between gastric hyper-activity and the development of these peptic ulcers. We are inclined to lay down the following as essential factors in the process:

(1) A local area of necrotic or necrescent mucosa.

(2) This area must correspond with the area of distribution of one of the terminal branches of a gastric artery in which either primarily or secondarily there is arrested circulation—primarily through embolic or other occlusion of the artery, secondarily through stasis and throm-botic change induced either by some local irritant, or, it may be, by the action of the hyperacid gastric juice acting on a submucosa deprived of its overlying epithelium, and rendered susceptible to the action of the gastric juice by inflammation.

(3) A normal, or, preferably, hyperacid gastric juice.

It may be asked why a generalized inflammation of the gastric mucosa is not followed by extensive peptic ulceration. The answer is that generalized inflammation leads constantly to the production of a gastric juice of diminished activity and digestive power. For the production of peptic ulcers the gastric mucosa in general must be normal,

if not producing a juice of heightened digestive capacity, and with this there must be some local focus of lowered vitality.

In connection with necrotic changes attention may be directed to the specific effects of different caustic agents upon the stomach wall. Thus caustic alkalies lead to a pronounced gelatinous or slimy swelling and softening of the mucosa. Sulphuric acid to a dry leathery appearance with grayish-black discolorations. According to its concentration nitric acid gives a pure yellowish staining or a yellowish brown. Carbolic acid causes whitish eschars, oxalic acid grayish-white discoloration, corrosive sublimate also a grayish-white superficial precipitation, copper sulphate a greenish discoloration.

Progressive Changes.—We have already referred to simple hypertrophy as seen in the pylorus. Here we would add a note of caution that some cases, possibly the larger proportion, of so-called pyloric hypertrophy of later life are not true hypertrophies, are not, that is, examples of overgrowth of the main tissue, in this case of the pyloric muscular ring, but are due to fibroid hyperplasia either of inflammatory or cancerous origin. We have, that is, encountered cases of pyloric thickening and stenosis in which only the most careful study has revealed rare collections of atrophied cancer cells. They have been cases of arrested scirrhous cancer in which the excessive growth of the fibrous stroma has choked and killed off the specific carcinoma cells.

Of benign growths, submucous and subserous **fibromas, lipomas,** and **neurinomas** (neurofibromas) are occasionally encountered, as are **myomas.** More common are simple **adenomas.** We have already indicated that multiple polypoid overgrowths may be secondary to inflammation (gastritis polyposa) or may be blastomatoid, hereditary in nature. There can be little doubt nowadays that such adenomatous overgrowth may precede and give place to true carcinoma.

Carcinoma.—This subject of carcinoma of the stomach is of high importance. There is indeed no organ more liable in both sexes. Thirty per cent. of all cases of carcinoma involve and indeed originate in this organ.

According to the form so do the symptoms and course vary. Thus we may encounter:

1. **Squamous-celled carcinoma** (epithelioma), comparatively rare, present at the cardiac end of the stomach and extending from the cardiac orifice. There the squamous epithelium of the œsophagus interdigitates to some extent with the columnar epithelium of the stomach and small processes more or less isolated may come thus to be present in the stomach wall. We presume that it is from such that this form of carcinoma has its origin.

2. **Adenocarcinoma** may be derived as a malignant transformation of the polypoid adenoma and present itself as a fungating polypoid or cauliflower-like mass projecting into the lumen of the stomach. The central portion of such a growth is singularly apt to undergo necrosis

and ulceration and originate severe hemorrhage. The more fungating forms of these growths are seen in the mid zone of the stomach. But while projecting inwardly there is coincident infiltration and invasion of the underlying tissues, and according to the tissue reaction and growing power of the aberrant gland cells so there may be varying proportions in the abundance (and size) of the cancer cells and the stroma. We thus encounter either (a) **medullary cancer**, abundantly cellular with large cells and great tendency to fungate; (b) **carcinoma**

Fig. 298
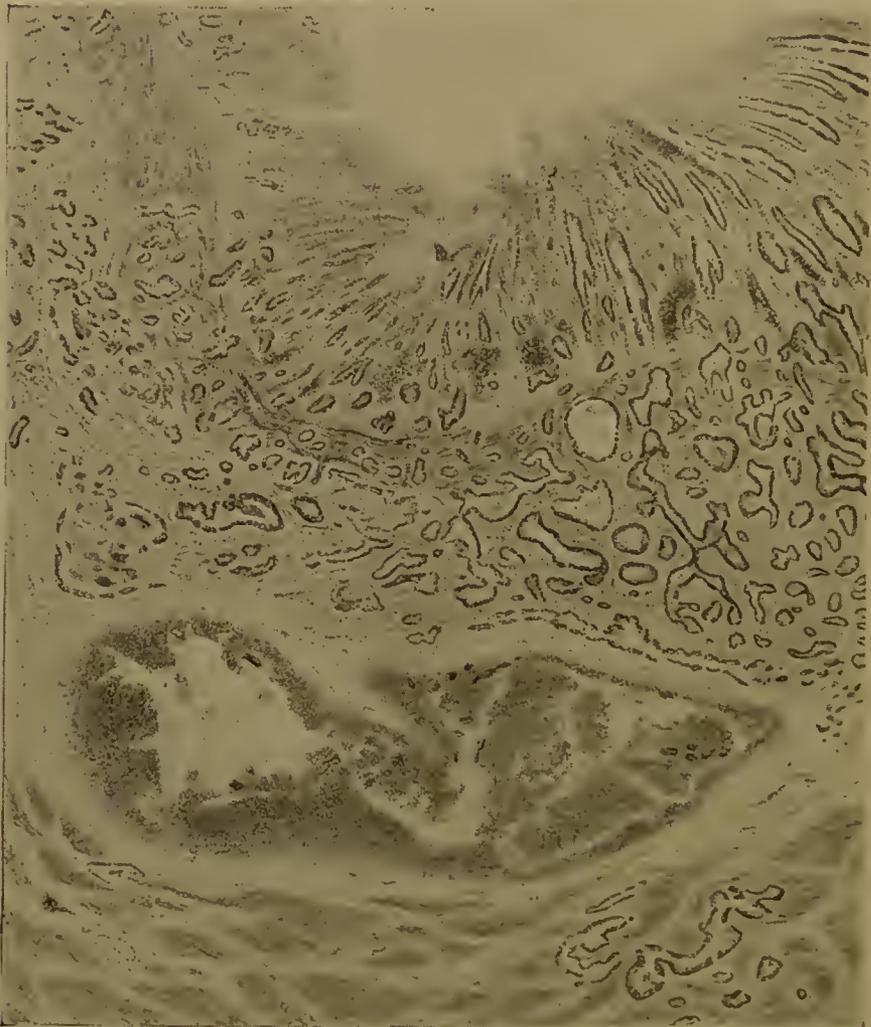
Adenocarcinoma of the stomach. The muscularis mucosæ and submucosa are pierced in all directions by carcinomatous tissue. An area of necrosis is seen in the lower part of the figure, between the muscular coat and the greater part of the new-growth. (Letulle.)

simplex; (c) **scirrhous cancer** with relatively small cells, abundant stroma, with little tendency to fungate, slower growth, less ulceration, although this eventually develops, and great tendency to infiltrate. The cancer cells in this form show the greatest departure from type and least indication of glandular relationship, lumen formation, etc. This scirrhous form is most common in the pyloric region, beginning often a little above the pylorus, not extending into the duodenum but infiltrating all the walls of the stomach from the pyloric toward the cardiac

end. This form may also originate in the lesser curvature. It appears to be related not so much to polypoid growths as to previous elceration.

3. A rare form with extensive infiltration is the **colloid cancer**, in which the cells of the adenocarcinoma retain their power of mucin formation, and the cancer alveoli become converted into inspissated masses of mucin, the cells undergoing a mucinous transformation to such an extent that they may not be recognizable, being completely disorganized and replaced by colloidal material. This form has extensive infiltrative power, invading the peritoneal and neighboring tissues.

Of these different forms it may in general be laid down that the more cellular the growth the greater the size of the primary mass and the more rapid the development of metastases. A densely scirrhous cancer of the pylorus may exhibit widespread extension through the stomach wall; indeed, the whole organ may become involved, and as a consequence be converted into a dense, thick-walled, shrunken tube, and nevertheless there may be little extension beyond. In this same scirrhous form, if metastases do occur they may grow much more rapidly and attain much greater size than the original growth. Thus we have seen a secondary growth in the liver the size of an infant's head, with a primary growth at the lesser curvature at the site of an old healed ulcer, so small as only to be discovered by careful search. The commonest site for secondary growths is in the lymph nodes situated outside the lesser curvature, next in the node or nodes above the head of the pancreas in the gastroduodenal angle, this last more particularly in cancer of the pylorus. Of other organs the liver is most frequently involved, either by direct extension or through the blood stream, and next most often the pancreas, by direct extension; similarly the gastrocolic and great omentum are apt to be invaded and to become contracted and thickened in consequence.

The most striking clinical feature accompanying gastric cancer is the loss or diminution of free acid in the stomach contents.

Sarcoma.—Primary sarcoma of the stomach is a much less frequent event, as is also secondary cancer, although the stomach wall is a not infrequent seat for secondary melanotic growths and we have seen a few cases in which it has been involved in lymphosarcomatosis.

THE INTESTINES

General Considerations.—From its size we are naturally led to regard the stomach as the most important section of the digestive tract, but this is an incorrect conclusion; the size is merely an accompaniment of its function, that, namely, of storing, kneading, and dissociating the masses of solid food until they become converted into a more finely divided state. Comparatively little assimilation takes place from the stomach, indeed, complete removal of the organ is perfectly compatible with continued existence. The main absorption of foodstuffs occurs in the small intestine. Anatomically and functionally we distinguish three sections

of the bowel: (1) the short **duodenum** receiving the hepatic and pancreatic ducts, in which the acid chyme becomes intimately admixed with the bile and pancreatic juice and rendered alkaline, before it passes on to (2) the **small intestine** in which, through the combined action of bile, pancreatic juice, and succus entericus all the various constituents of the food, proteins, carbohydrates, and fats are rendered soluble and assimilable; (3) the **large intestine** whose function is in the main to inspissate the unutilized remains of food and store them until such time as they become voided. Judged from its structure the upper half of the small intestine, the **jejunum**, with its pronounced increase of surface (the rugæ) is the more active region of absorption; the greater amount of lymphoid tissue in the **ileum** in the shape of solitary follicles

Fig. 299
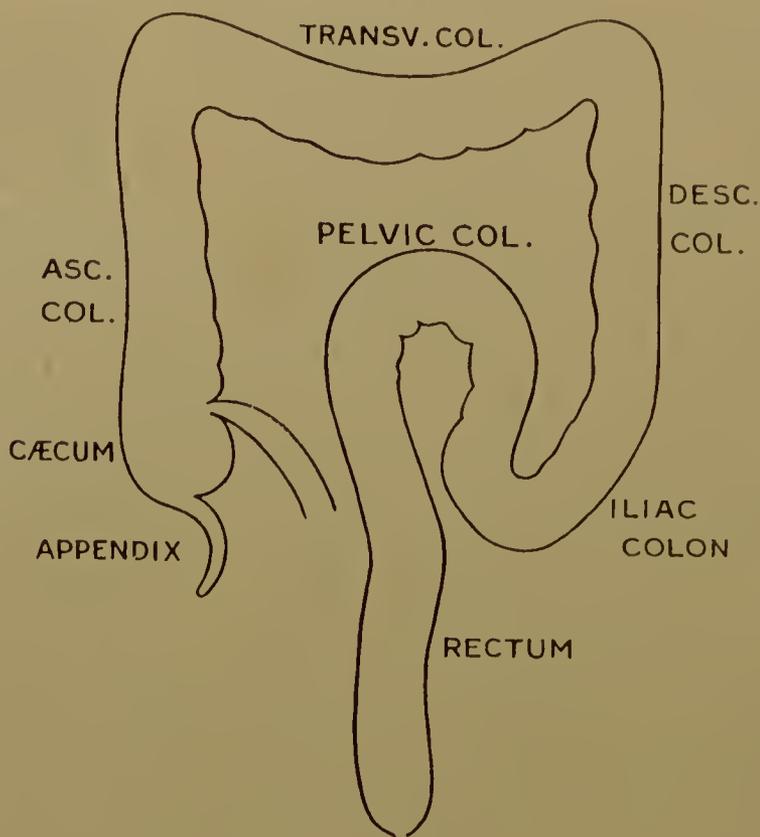
and Peyer's patches is correlated with the need for protection against the abundant bacterial flora of this part of the tract and against the products of bacterial activity. The large intestine also has its divisions —appendix, colon, and rectum. It is usual to regard the **appendix** as a useless rudiment, basing this view upon its great variation in size. To this view we cannot agree; complete absence is as rare as is complete absence of the stomach, and that organ also exhibits marked variation in size. No one, however, suggests that the stomach is a useless and disappearing organ. Rather, we cannot but be impressed by the hydrostatic relationships of the large gut in man, an erect animal.

The fluid contents of the ileum pour into the cæcum and there and in the ascending colon undergo inspissation prior to discharge *per*

anum. In other words, the cecum and ascending colon have physiologically to undergo great variation in the volume of their contents. It would be to the detriment of their function were they to be acutely susceptible to pressure changes, were they to undergo peristalsis and void their contents immediately they became filled from the ileum. We must regard them thus as, in the normal state, distinctly unresponsive to pressure effects. It is the appendix, we hold, that is the hydrostatic agent initialling peristalsis in the large gut. In it we have a narrow tube, with no such pronounced variations in caliber, so situated that the weight of the column of forming feces is communicated to it, and we presume that when this weight reaches a certain point, the distending force acting upon its walls originates muscular contractions which spread directly into the cecum and so initiate the forward movement of their contents. Such a view explains the tendency to constipation in the bedridden, in whom this gravitational influence of the contents of the ascending colon can have little effect; it explains the normal tendency to empty the bowels, either shortly after rising and assuming the erect position or after the first meal when stimulating peristalsis of the small bowel has driven extra contents into the cecum and so increased the load; it explains the constipation that follows some interval removals of the appendix.

At the other end of the colon we have another hydrostatic mechanism. In normal health the rectum is empty until immediately preceding the act of defecation. As Hertz has shown, that act is brought about by the sensitiveness of the preanal portion of the rectum to internal pressure, but this sensory mechanism becomes soon exhausted if the pressure continues, if, that is, the call to defecate be not attended to. Once, therefore, the rectum is loaded and not duly emptied it is apt to become overloaded. This rectal constipation with all its attendant ills and miseries is guarded against by the siphon action of the sigmoid flexure. The formed fecal matter does not gradually dribble into the rectum; it gradually accumulates in the descending colon and the proximal limb of the flexure until a column is formed of sufficient length to set up the pressure necessary to surmount the curve and once around the curve the whole column siphons rapidly into the rectum. Once there it exerts sudden pressure upon the anal region and demands discharge.

Constipation.—It will be seen that constipation may be of various orders: (1) **obstructive**, from kinks, contractures, etc., of one or other portion of the gut, arresting the inflow of the contents. (2) **Fecal inadequacy**, when either from starvation or from the ingestion of easily absorbable or predigested foods, sufficient indigestible remnants are not afforded to possess by their volume a hydrostatic effect. In such cases hardened feces accumulate more particularly in the cecum and sigmoid. (3) **Atonic**, when either (*a*) the sensory limb of the reflex arc is exhausted or depressed and pressure within the gut does not excite peristalsis as in rectal constipation or (*b*) through previous distension or disease the musculature fails to respond. (4) **Appendical,**

through lack of initiation of colonic peristalsis either from inflammation or other obliteration of the lumen of the appendix or operative removal of the same.

Diarrhœa and Dysentery.—Diarrhœa is the broader term indicating the discharge of watery non-inspissated bowel contents; dysentery[1] the narrower, indicating a like passage accompanied by tenesmus, pain, and straining. Not only this, but discharges of this type are commonly due to inflammation of the large gut and are accompanied by the passage of increased mucus with some blood. Diarrhœa, on the other hand, more often (although not essentially) originates from disturbed conditions in the small intestine. With this of necessity there must be failure on the part of the large intestine to absorb the fluid pressed into it from the ileum. That failure, however, need not be due to a disordered state of the large gut. More frequently it would appear that the contents of the small bowel enter the colon so rapidly and in such abundance that the hydrostatic mechanism is set in action and the very weight and distending effect of the abundant matter induces peristalsis and rapid discharge.

These watery feces may be of various orders and due to:

1. Excessive intake of fluid, although, as in the infant, this more often causes soft feces than diarrhœa proper.

2. Hypertonicity, and here again either (*a*) the sensory limb of the reflex is unduly irritable or susceptible of stimulation and induces a corresponding excessive peristalsis. Here we may deal with a reflex set up by abnormal contents of the bowel or by reflex or other sensory stimulants, or (*b*) the intestinal musculature may be unduly responsive. In either case we deal not with the discharge of increased local contents, but the premature expulsion of imperfectly acted upon and non-inspissated matter.

3. Excessive discharge of fluid through the intestinal wall. The type example of this form is seen in cholera where the growth of the spirillum upon and in the mucosa induces an intense congestion and exudation of fluid from the capillaries, until the rapidly recurring motions come to consist of little beyond serous fluid with shreds of necrotic mucosa, and consequently the blood becomes extraordinarily diminished in amount and tarry in consistence. Saline purgatives similarly attract fluid into the bowel.

Speaking thus of excretions from the bowels it deserves here to be recalled that the digestive tract subserves not merely absorption and assimilation of foodstuffs but also the elimination of sundry toxic substances—mercury, for example, from the salivary glands, antimony from the stomach, as also along with mercury from the colon. It is the abnormal and excessive discharge of these toxic substances, as again of the (unknown) toxic substances which become heaped up in the system in the uremic state, which lead to necrosis and ulceration of the colon.

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[1] δύς, hard (*i. e.*, difficult), ἔντερον, the bowel.

Recently, Hiss has demonstrated conclusively that bacteria are discharged from the circulation into various portions of the gut, and this after ligature of the common bile duct.

Abnormalities.—Apart from considerable variations in length, the most common abnormality is the presence of **Meckel's diverticulum**, or the persistent remains of the proximal part of the omphalomeseraic duct. There may be various grades of the persistence from the complete duct opening at the navel (very rare), through the state in which a fibrous band adherent at the navel represents the distal portion and passes into a diverticulum opening off the ileum and lined with mucosa, representing the proximal portion. The most frequent condition is a finger-like free diverticulum, one to three inches in length, with or without a mesentery of its own, given off from the ileum from thirty to forty inches above the ileocecal valve. We have encountered this in 2.7 per cent. of our autopsies. Belonging to the same system are occasional abdominal **cysts** representing a persistent intermediate part of the duct, and the condition of persistence of a congested moist columnar epithelium upon the navel, or it may be an actual blind sinus leading down from the same. More particularly where there is a fibrous band of attachment, the diverticulum may become the cause of internal hernias with strangulation of coils of the intestine. We shall refer later to the acquired diverticula.

The appendix in addition to variation in length may be abnormally placed, infrequently retroperitoneal.

Another important condition of congenital origin is congenital hypertrophy of the sigmoid and often of the colon—**megacolon (Hirschsprung's disease)**. In this there is noted in the young child a progressive enlargement of the abdomen until it attains huge size, and associated with this there is progressive constipation.

On opening the abdomen the sigmoid is found of relatively enormous size, occupying the greater part of the cavity. There may or may not be associated enlargement of the descending colon, or the colon in general, and with this pronounced hypertrophy of the coats. There has been much discussion as to the causation. In two well-marked cases seen by us there was an abnormal mesentery of the sigmoid; the lower end of the descending colon was closely bound down by the peritoneal attachments, and gave place to a large, fan-like mesentery of the sigmoid proper, with similar binding down of the sigmoid-rectum junction, a condition favorable to obstruction by kinking when the sigmoid became loaded and so to its progressive distension. One of the two cases had a similar close binding down at the splenic flexure with corresponding dilatation and hypertrophy of the transverse colon. Others, however, deny the evidence of this primary and anatomical defect, and possibly there exists another order of cases in which not potential obstruction but primary atony of the walls is the fault.

The third important group of abnormalities is that of the **stenoses** and **atresias**. The presence of membranous septa occluding the duo-

denum has been reported (corresponding to the end of the meso-gastrium anterius), in the ileum (corresponding to the region of exit of the omphalomeseraic duct), etc., together with contractures and stenoses that can only be explained as the after results of antenatal peritonitis. The most frequent set of cases is constituted by the various orders of **atresia ani** and **atresia recti,** due respectively to persistence of the cloacal septum and to lack of descent of the rectum to come into apposition with this.

Acquired Anomalies.—Here it will be useful to pass rapidly in review the more important of the changes in form and position of the intestines.

Two orders of acquired **dilatation** are to be kept in mind: (1) obstructive; (2) paralytic. The former shows itself above any region of obstruction whether by stenosis, kinking, volvulus, or impaction of fecal matter and, if of general development, is associated with hypertrophy; the latter is seen in peritonitis and acute infections (typhoid, pneumonia, etc.); it is evidently the result of the action of bacterial toxins upon the musculature of the bowels or else is the result of a distension so great that the stretched muscle fibres are unable to begin the necessary contraction. The latter seems to be the case in those instances where peristalsis is at once resumed after the gas has been let out by a trocar.

Diverticula.—Acquired local dilatations of the bowel wall, diverticula, are not infrequent in the duodenum and there particularly in the neighborhood of the ampulla of Vater; in the small intestine they present themselves at the region of greatest weakness of the wall, namely, where the branches of the mesenteric artery penetrate through the circular muscle, and when coincidently the mesentery divides to encircle the gut. They thus constantly show themselves at the mesenteric attachment; they may be multiple and the size of a pea or even of a cherry. More common, especially in elderly people, are diverticula of the colon. They occur in the weaker regions intermediate between the longitudinal muscle bands and may be very numerous. They are of the nature of small hernias of the mucosa and submucosa between the circular muscle fibres, have little or no muscle in their walls but an outer coat of the serosa. They occur when atrophy of the muscle is favored, in cases of chronic constipation and when, through rapid disappearance of the subserous fat, the wall becomes weakened. Occasionally these become the seat of inflammation (**diverticulitis**) with excessive small-celled infiltration.

Volvulus or the twisting of a loop of intestine upon itself may affect either the loose sigmoid flexure or the small intestine. It leads naturally to obstructive phenomena, as also to intense congestion of the twisted loop, followed, if the twist be not released, by gangrene.

Such **strangulation** may be brought about, however, by many other means—by the snaring of a loop of intestine in a hernial sac, or between adhesions and bands in the peritoneal cavity, or by invagination. In all these cases the weaker veins are compressed before the arteries and

then occurs a progressively increasing congestion of all the walls followed by stasis, necrosis, and gangrene.

Invagination (intussusception) is brought about by irregular peristalsis, or more accurately, incoördination between the contractions of the longitudinal and circular muscles, whereby a part of the gut above is either projected into the segment immediately below or is caught by that lower segment in its contraction. As a result, once caught within, the peristaltic contraction propels it downward just as if it were a fecal mass within the lumen. In this way long segments of the bowel may become invaginated within the portion of bowel below, and may indeed appear at and be projected through the anus. It will be realized that the attached mesentery likewise becomes invaginated, with compression of its vessels, congestion and liability to gangrene. Inflammatory adhesions are apt to form at the reactive upper end of the invagination and thus the **gangrenous intussusception** may rot off without there being escape of feces at the line of junction. In such cases a zone of stenosis in the shortened bowel may be the outcome of the process. In other cases, unless operated upon, the obstruction and toxemia may lead to death, or there may be peritonitis from perforation.

These invaginations may involve the ileum alone (ileal), or, at the valve, the ileum may become invaginated into the cecum (ileocecal), in which case the cecum and appendix may also be carried forward to form part of the intussusception; may be colic, affecting the colon alone, or colicorectal, the colon becoming invaginated within the rectum.

This irregular peristalsis occurs most often in young children, and in them therefore invagination is most frequently encountered. As a curiosity we may encounter one invagination setting up a second invagination below, and so presenting not three but five coats; or, again, through reverse peristalsis the invagination may occur in an upward direction.

Such reverse invagination is most frequently seen in the condition of **agonal invagination.** Often at autopsies, more particularly upon children, small invaginations of the small intestine present themselves, evidently due to irregular peristalsis during the death agony or in the hour or two immediately succeeding death. They differ from the other cases in their tendency to be multiple (three or more), in their small size, in the absence of any signs of inflammation of the serosa, and in the case with which they can be reduced.

Circulatory Disturbances.—The great vascularity of the intestinal mucosa renders it apt to react in a very pronounced manner to altered circulatory states; it shows extreme pallor in cases of general **anemia,** intense acute **hyperemia** in inflammatory states, and even more marked engorgement and purplish coloration in conditions of passive hyperemia, such as follow partial or complete obstruction of the portal vein or its mesenteric branches, or obstructive cardiac disease. In this passive congestion the subserous veins stand out prominently; the mucosa assumes a bluish-purple color, is swollen and succulent through

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œdematous transudation, and, as already noted in connection with the stomach, if the condition is of some duration there are evidences of a secondary and accompanying low inflammatory state.

Hemorrhage.—Where the hyperemia is acute, whether active (infective) or passive, there may be submucous hemorrhages from the capillaries followed by hemorrhagic erosions, although these are not nearly so common as in the stomach. Other causes of hemorrhage are trauma, hemophilia, vicarious menstruation, malignant growths, ulceration (typhoidal, dysenteric, etc.), and hemorrhoids. Blood escaping into the lumen of the upper part of the bowel becomes tarry owing to dissociation of the hemoglobin and action of the sulphuretted hydrogen of the feces. There may be long-continued oozing of small quantities from the stomach or intestines, which becomes so concealed by the natural color of the feces as to be unrecognizable, save by delicate blood tests (**occult hemorrhage**).

Hemorrhagic Infarcts.—There is extensive serial anastomosis of the branches of the superior and inferior mesenteric arteries, but this is frequently inadequate to afford rapidly a sufficient collateral circulation where an important branch of either artery becomes blocked by an embolus or otherwise obliterated, and, as a result, there may be infarct formation. This, in our experience, is more common in the small than in the large gut. The result varies in extent from one to forty inches and more, according to the importance of the artery that has become blocked, or, expressed otherwise, the distance of the lesion from the intestine. It varies in appearance according largely to the length of time that elapses before death ensues. In the early stages the affected length of gut seen from without is of a bluish-purple color and on opening presents an intensely congested thickened and hemorrhagic mucosa. Later the inner superficial layers may become broken down with oozing of blood-stained matter, and later still the whole thickness of the necrosed mucosa and muscular coat may slough or be digested away until, as we have seen in one case, merely the distended serous coat may be left over a considerable area, and this in turn may give way, liberating the contents into the abdominal cavity. Similar infarct formation may result from thrombosis and other forms of obstruction of the larger mesenteric veins and, in fact, an identical process due to venous obstruction is seen in volvulus and strangulated hernia—intense congestion with stasis, hemorrhage, necrosis, and gangrene.

Hemorrhoids.—**Varices** of the congested superficial veins may occur although they are not so common as in the stomach. An exception, however, must be made for a local development of what are essentially varicosities and are as painfully common as they are commonly painful. We refer to hemorrhoids (**piles**). These are due to the interaction of several factors: (1) a state of passive congestion of the rectal and anal veins; (2) to the superficial, poorly protected nature of the anal veins; (3) the increased congestion of these vessels induced by the act of straining at stool and (4) in external piles, the obstruction to the

emptying of the distended vessels which results upon the subsequent firm contraction of the sphincter ani. The result is the production of a more or less complete circle of projecting varicose vessels at the anal ring, external to the sphincter, which are apt to be irritated and eroded by the passage of hard fecal matter, which may undergo rupture and so induce severe hemorrhage, or from which, again, there may merely be oozing of blood; or, lastly, the contained blood may undergo thrombosis, and some organization.

Peptic and Necrotic Ulcers.—True peptic ulcers are now well recognized by surgeons as by pathologists as occurring frequently in the first part of the duodenum. Ulcers of similar nature, produced by digestion of small areas of necrosed mucosa are rare in the small intestine, although they may occur, at times due to infarction of the area supplied by a terminal arteriole, or thrombosis of a small mesenteric vein.

Fig. 300
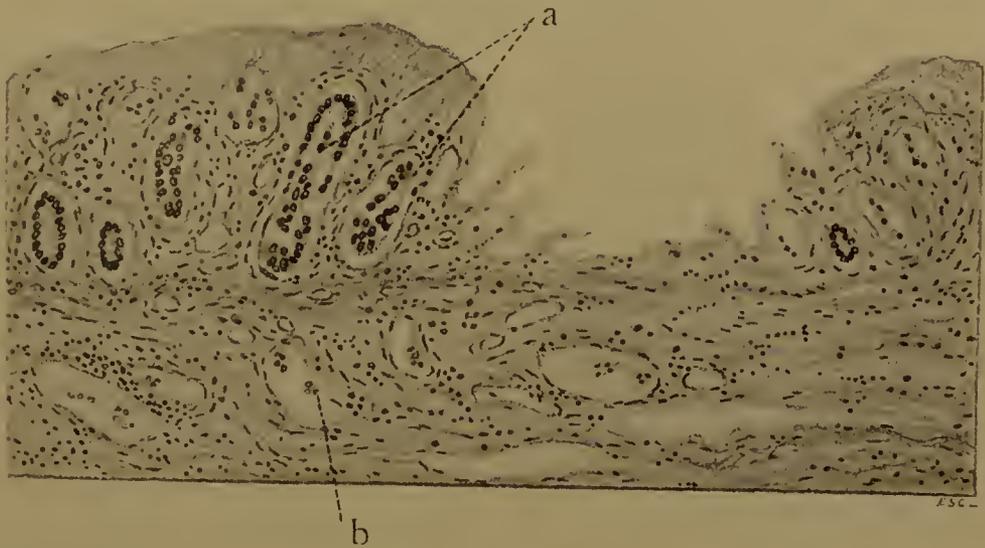
Section through a small simple necrotic ulcer of ileum, involving only the mucosa: *a*, Lieberkühnian follicles; *b*, congested vessels of submucosa.

Inflammation.—Different names are given to inflammatory disturbances according to the region affected—**duodenitis, enteritis** (of the small bowel), **appendicitis, typhlitis** or **cecitis** (of the cecum), **colitis, proctitis** (of the rectum).

Owing to post mortem digestion of the superficial layers it is by no means easy to gain satisfactory histological pictures of the various forms of inflammation involving especially the mucosa. There may have been all the clinical evidences of an acute enteritis, but very little may manifest itself on microscopic examination that can surely be ascribed to acute inflammation. This is particularly true of simple or **catarrhal enteritis** and **colitis.** If the mucosa be well retained it may show an excessive number of goblet cells. The submucosa also may present pronounced congestion and extensive leukocytic infiltration, but the same hyperemia and leukocytosis are features of certain stages of digestion and some experience is needed to determine

whether these exceed the normal limits. Petechial hemorrhages suggest an abnormal state, but superficial necroses accompanying these are difficult to distinguish from areas of more extensive post mortem digestion.

Occasionally, however, the infiltration of leukocytes between the Lieberkühnian crypts is so extensive that there need be no doubt; indeed, the condition may be so pronounced as to constitute a suppurative infiltration of **phlegmonous** type with a tendency to necrosis of the overlying mucosa and ulceration. This is uncommon.

Follicular enteritis and **colitis** also present difficulties. Particularly in children it is not unusual to find the solitary follicles of both small and large gut so much enlarged that they stand out prominently. Is this of inflammatory origin or does it merely mean an enlargement of the lymph follicles which is part and parcel of the lymphoid hyperplasia common in childhood? When the follicles are surrounded each by a zone of congestion we incline to an inflammatory causation, and when, in addition, the condition is encountered after adolescence and there is evidence of erosion over these small nodes and actual ulceration, the diagnosis becomes still more assured. It is more particularly in the colon that we encounter such folliculitis in the adult, while in children in diphtheria and other acute infections the solitary follicles in the small bowel may be so prominent that the condition must be regarded as of inflammatory type.

Fig. 301

Lymphoid hyperplasia of ileum in a child, leading to the production of a polypoid state. (McGill Path. Mus.)

Membranous enteritis, superficial necrosis of the mucosa with coagulative membrane formation, is occasionally encountered, most often in the cæcum and colon, and lower end of the ileum, either diffuse or in patches over the rugæ and more projecting portions of the mucosa. With deeper extension of the necrotic process and sloughing of the membrane, extensive ulceration may ensue. The condition is well seen in mercury and arsenic poisoning, and uremia, and, combined with extensive ulceration of the large bowel, in both amœbic and bacillary dysentery. Prolonged retention of feces may lead to a combination of membranous and ulcerative colitis, occasional ulcers resulting of small size, which originate apparently from the lymph follicles.

Special Forms of Intestinal Inflammation.—**Typhoid Fever.**—The commonest lesion in typhoid fever is an involvement of the Peyer's patches in the ileum above the ileocecal valve; we may, however, encounter cases with no recognizable affection of the intestinal lymph nodes, others in which the solitary follicles of the colon alone are affected. We have seen one case in which the solitary ulcer was in the appendix,

although before death the blood gave the Gruber-Widal reaction and after death pure cultures of typical typhoid bacilli were gained from the blood and peritoneal contents. But these are rarities. The site of election of the disease is the last two feet or more of the ileum and there, the contained Peyer's patches. These may, it is true, be involved throughout the whole length of the ileum and with them the solitary follicles. So, also, in quite a considerable proportion of our cases in Montreal (no less than 32 per cent.) the solitary follicles in the cæcum, colon and, in a few cases, the rectum have been simultaneously affected, nor does the severity of the case and the toxic state appear to have any definite relationship to the extent of involvement of the lymph patches. It may be that the lower part of the ileum and the rectum are affected the more because at these points there is a greater arrest of contents than elsewhere.

The stages in the development of the typhoid lesions are the following: (for the general course of the disease see p. 141.)

I. *Stage of Tumefaction.*—It is rare to meet with cases in which death has occurred before the end of the first week of fever, but where it has taken place from the seventh to the tenth day, the Peyer's patches and adjacent solitary follicles are found greatly swollen, standing out well above the level of the rest of the mucosa, either exhibiting some congestion or distinctly pale and anemic. Since all are not involved at the same time, but commonly those nearest to the valve are earlier affected and others more remote exhibit earlier stages, it is at times possible by the study of one case to follow the various stages. Of these the earliest is seen to be an acute hyperemia with moderate swelling of the Peyer's patches. Sections exhibit the individual follicles surrounded by a hyperemic zone, and the peripheral lymph spaces filled with large cells of the endothelial type (macrophages). These are actively phagocytic and may contain leukocytes and red corpuscles and their remains. The individual follicles are large and show evidences of active proliferation of lymphocytes. At a later stage the lymph spaces are found intensely engorged with these large cells, which replace the previous small, round-cell areas of the individual nodes, the picture suggesting strongly that both the mother cells of the centres of the nodes, and it may well be the small lymphocytes themselves undergo conversion into the larger type of cell. The affected patch or solitary follicle becomes now so tensely packed with these cells as to be rendered anemic and pale.

II. *Stage of Necrosis* (from about the twelfth to the nineteenth day).—In nodes showing the anemic swelling many of the "macrophages" show signs of degeneration and death, but this becomes progressively more marked, and now masses of these cells corresponding to the centres of individual nodes undergo a necrosis, which involves the stretched overlying mucosa. These dead areas become stained with fecal pigment, and begin to slough out. Where the process is widespread throughout a patch, there may be a striking appearance
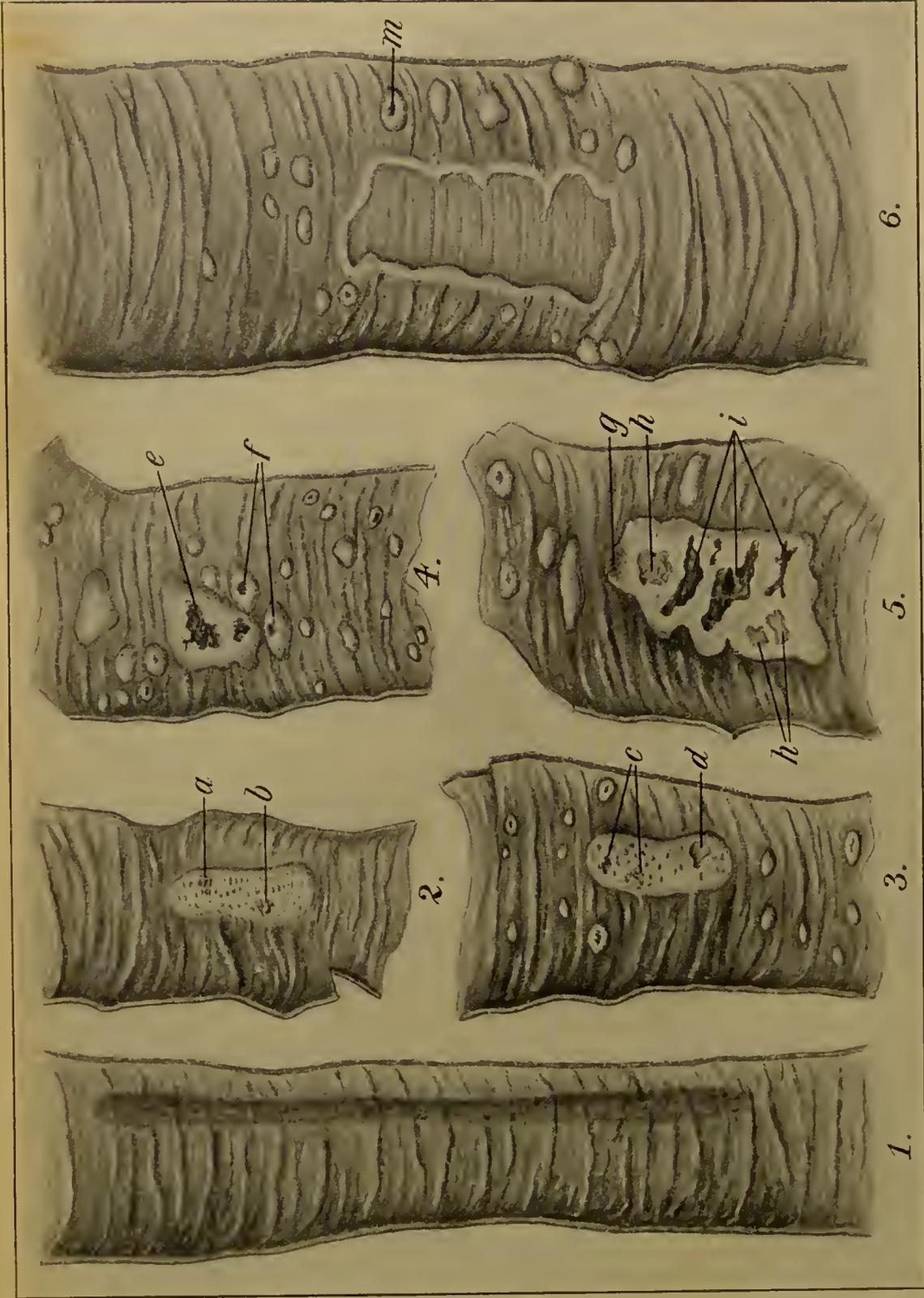
FIG. 302

Typhoid fever. Peyer's patches and solitary follicles from a youth, aged twenty years, to show the successive stages (P. M. 31-08 Royal Victoria Hospital.) 1. Abnormally long Peyer's patch (16 cm.) showing congestion and slight swelling, in commencement of ileum, 250 cm. from valve. 2. Patch of normal size, situated a little lower down, 225 cm. from ileocæcal valve, showing *état criblée*, and at *a*, small area of hemorrhage; at *b*, another hemorrhagic area, with central pale-staining area of necrosis. 3. Patch, 210 cm. from valve. Here the solitary follicles also show swelling; at *c*, hemorrhagic areas with necrotic centres; at *d*, a loosened slough or necrotic area, bile stained. 4. Peyer's patch, some 50 cm. lower down, with two sloughing areas, that at *e*, loose and almost detached; at *f*, solitary follicles, with necrotic centres. 5. A patch midway between the last and the ileocæcal valve; *g*, hemorrhagic area; *h*, slough becoming loosened; *i*, ulcerated areas. from which the sloughs have escaped. 6. Large Peyer's patch, a few cm. above the valve, showing the completed ulcer. The whole patch has sloughed away, exposing the circular muscular coat of the bowel; *m*, solitary follicle that has ulcerated. There were ulcers also in the appendix, cæcum, and ascending colon.

produced; the small isolated sloughs may have dropped out, leaving the patch riddled with small irregular perforations (**état criblée**). It deserves note that the whole of a patch would not seem necessarily to proceed to this stage of necrosis so that we may meet with patches in which the sloughing affects only one portion.

III. *Stage of the Developed Ulcer* (nineteenth to twenty-eighth day).—The necrosis and sloughing once manifested tend to involve the whole of the affected individual node, so that large pigment-stained sloughs may be formed. In typical cases the whole of the lymphoid tissue constituting the Peyer's patch sloughs away leaving an ulcer having the following characteristics: (1) a clean, smooth floor with fine transverse ridging, formed of the exposed circular muscle; (2) raised overhanging edges formed of the intact mucosa of the margin of the patch from beneath which the lymphoid tissue has sloughed out; (3) a long

Fig. 303
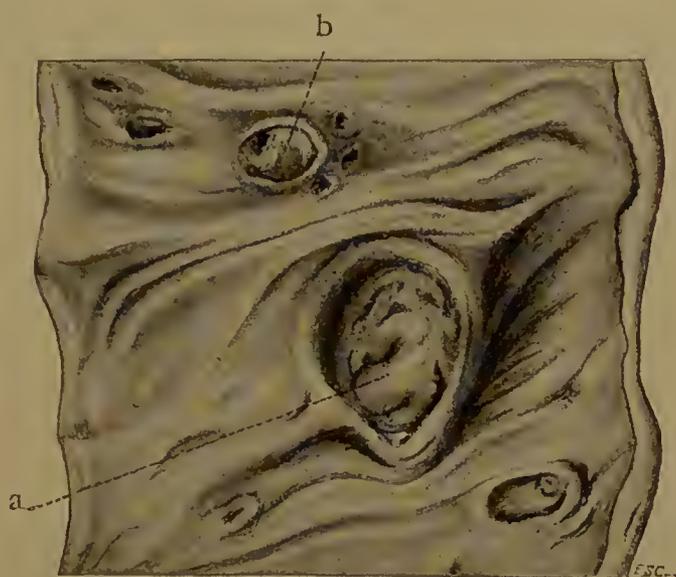
Ileum from a case of typhoid fever, showing ulceration of solitary follicles (*b*) and of a small Peyer's patch (*a*).

axis corresponding with the long axis of the ileum (although where part of a patch only undergoes necrosis the ulcer may be rounded or have a larger transverse axis); (4) a situation on the bowel wall remote from the mesenteric attachment. When solitary follicles are involved the ulcers are correspondingly smaller and circular; more particularly in the colon, they may, however, be so large as to suggest that not merely the lymph node but also the surrounding zone of submucosa has been affected by the necrotic and sloughing process.

IV. *Stage of Healing* (after the fourth week).—The overhanging, somewhat raised edges become flattened down and adherent to the floor, and now the mucous membrane, regenerating, covers that floor with a smooth shiny layer of epithelium. There is very little granulation tissue produced, and little or no subsequent contraction. Where death occurs a few months later all that is to be made out is a smooth, small, oval area where the wall is thinner than normal.

The figures above given are approximate; they refer to the condition of the oldest crop of affected nodes nearest to the valve. We repeat that cases are not infrequent in which these oldest ulcers are of the fourth week or later, whereas higher up in the ileum there may be Peyer's patches showing the changes characteristic of the end of the first week. Progressive involvement of lymph nodes explains the long-continued cases; where successive crops of nodes are affected at intervals we obtain **relapses**.

Similar necroses are liable to occur in the mesenteric lymph nodes; the lymph node situated in the ileocecal angle is constantly enlarged in typhoid and is particularly apt to exhibit whitish areas of necrosis.

The two grave complications of the typhoidal process are **hemorrhage** through erosion of a vessel or vessels in the sloughing stage, and **perforation**, either through extension of the necrotic process into the muscular layers, possibly along the lymph channels, penetrating that muscle, or through rupture following pressure of the bowel contents upon the weakened area. Most often the perforation is small, of the "pin-point" variety, suggesting the former mode of origin.

Tuberculosis.—Tuberculosis may involve any portion of the small and large intestines, and has no special site of election, save that where infected feces become arrested in the lower part of the ileum, in the cæcum, sigmoid, and rectum, there infection is most liable to occur. Although it oftenest originates in individual lymph nodes, there is not the same strong tendency to implicate primarily the nodes immediately above the ileocecal valve, and, what is more, in the subsequent stages the process spreads beyond the limits of the nodes and patches, involving all the coats.

The infection may be (1) of hematogenous origin (acute miliary tuberculosis; this rarely sets up extensive lesions), or (2) of enterogenous origin, from the bowel contents, or (3) peritoneal, by infection from the peritoneal fluid secondary to ovarian, tubal or other abdominal tuberculosis. This last will be discussed later. It is the enterogenous that causes the most characteristic lesions. This may be primary, from the food, and then most often set up by the bovine type of bacillus (milk), or secondary, due to swallowing of sputum where there exists pulmonary or laryngeal tuberculosis (human type). Saying this, it must be remembered that infection with the bovine type shows itself most often not in the intestinal wall but in the mesenteric nodes. It has been abundantly proved by experiment that the tubercle bacilli may be carried through the bowel wall without setting up any lesion, only becoming arrested in the mesenteric nodes. The bacilli carried through the mucosa may become arrested in the submucosa, and there most naturally in some lymph node or collection of lymphoid tissue along the course of a lymphatic. Thus there develops a submucous tubercle, and bacilli escaping or carried from this induce the formation of secondary tubercles in the immediate neighborhood. These in their growth fuse and undergo central caseation, cut off the nutrition from,

and even invade, the overlying mucosa, and necrosis and ulceration is the result. The subsequent stages are those of progressive extension of the lesion; new tubercles form especially along the course of the lymphatics and as these lymphatics, like the blood vessels, have a circular

FIG. 304
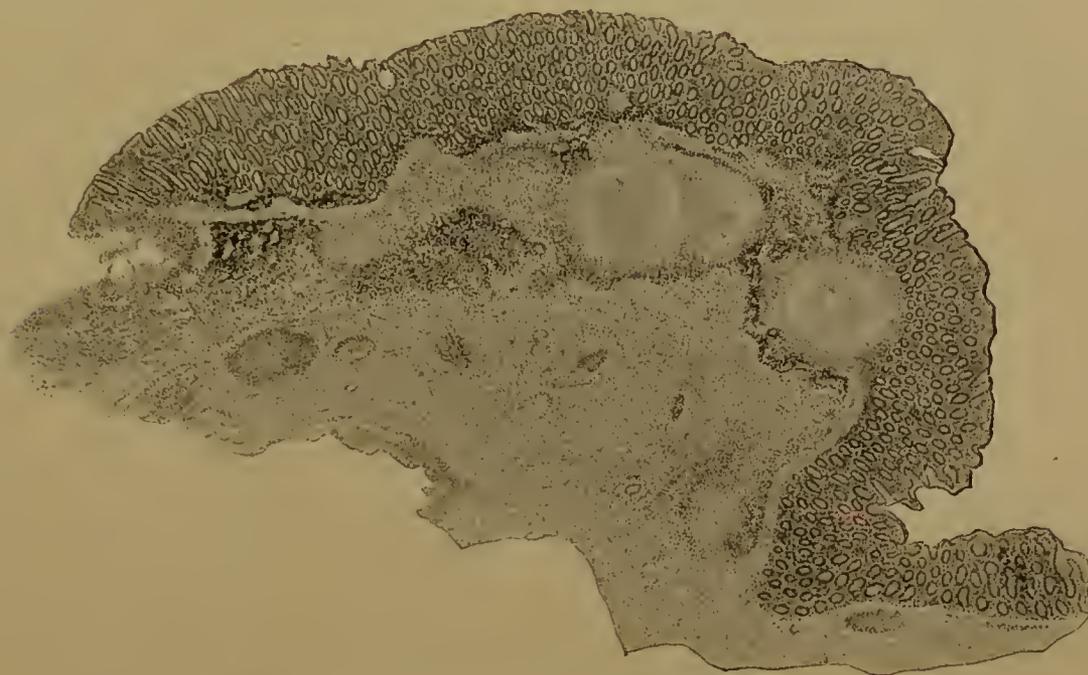
Submucous tubercles in large intestine. (Raubitschek.)

FIG. 305
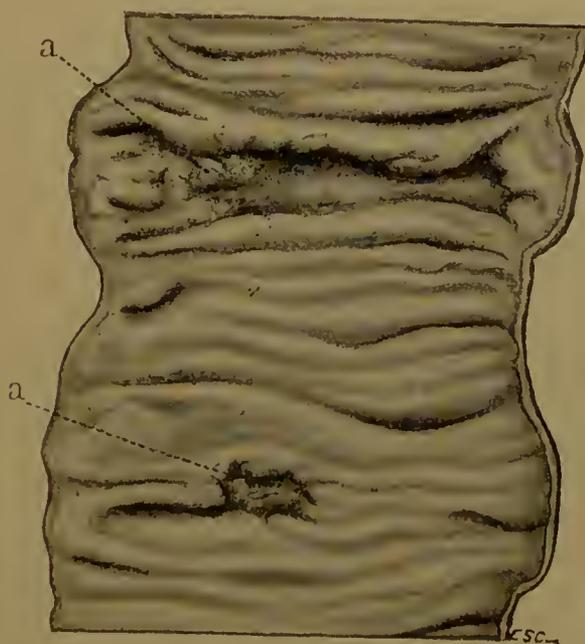
Tuberculous ulceration of the jejunum, showing ulcers (*a*, *a*) tending to be annular. (McGill Path. Mus.)

disposition, the tubercle formation and ulceration is peculiarly apt to be most marked in a transverse direction, often becoming completely annular. Other lymphatics penetrate the muscularis and thus simultaneously tubercles become formed on the serous aspect of the gut.

These groups of subserous tubercles are the first indication of the condition upon inspecting the opened abdomen.

From the nature of this process it follows also that the resultant ulcers have irregular edges irregularly swollen by the presence of underlying tubercles, irregularly undermined where these have undergone caseation, and that their floors, instead of being smooth as in typhoid, are nodose and irregular, formed of a layer of tubercles or of these alternating with caseating areas. This caseation and ulceration may extend into the muscularis, which forms no natural boundary. Where this extension is marked, there also is well-defined subserous tuberculosis, and, secondary to this, a notable tendency to the formation of local adhesions. These explain why in intestinal tuberculosis perforation and perforative peritonitis are comparatively rare, while the formation of fistulous communications between various segments of the bowel is comparatively frequent. We have encountered half a dozen of these in a single case. The disease is apt to be chronic and, what is more, to show healing, fibrosis, and contraction in one area, while in the immediate neighborhood new tubercles may be forming.

The largest of these annular ulcers are to be met with in the cæcum and colon.

Tuberculous ulceration involving the mucosal pouches formed by the contraction of the sphincter ani, leads to one form of **fistula in ano**.

Fig. 306
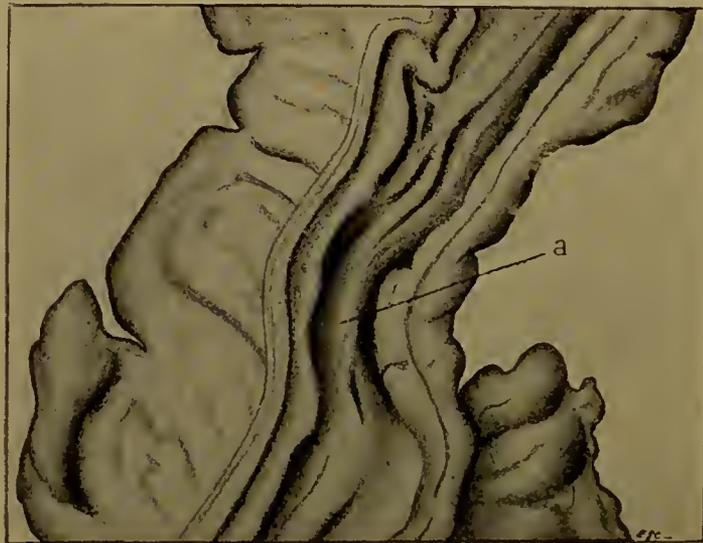
Syphilitic periproctitis. Portion of the lower end of the rectum, showing at *a* great contraction of the lumen, thickening of all the coats and extensive hyperplasia and fibrosis of the periproctal tissue. (McGill Path. Mus.)

Syphilis.—Save in connection with the rectum (and the characteristic lesions there are now coming, by some at least, to be regarded as doubtfully of syphilitic origin), acquired syphilis rarely affects the intestinal tract. A form of lesion is described as affecting more particularly the jejunum, in the form of groups of small nodes arranged in a circular manner in the submucosa which, under the microscope,

presents vessels with characteristic perivascular small-celled infiltration. The mucosa over these is apt to ulcerate, leading to transversely disposed, somewhat shallow ulcers with uneven pale floors.

What until recently was held to be a syphilitic proctitis and periproctitis is a remarkable condition of venereal origin, presenting a combination of ulceration and irregular hyperplasia of the rectal mucosa through the greater part of its course, with fistula formation and the production of periproctal abscesses. Sections show a pronounced plasma cell infiltration throughout, without the small-celled perivascular infiltration so common in syphilis being a leading feature.

The intestines are more frequently found infected in congenital syphilis. The commonest form is a diffuse small-celled perivascular infiltration of the submucosa and muscular coats, but the development of scattered gummas has also been recorded and, more frequently, of multiple miliary gummas of the submucosa and muscularis, closely allied, we may suggest, to the first form.

Appendicitis.—All the aspects of appendicitis are now-a-days treated in such full detail in the text-books of surgery, and the student is expected to have so thorough a knowledge of the subject that we find ourselves in a dilemma. To fulfil his needs, to discuss the etiology, classification, histology, and sequels on the same scale as does the surgeon would consume many pages and be out of balance with the treatment here afforded to other important conditions; to indicate briefly the main data may lay us open to a charge of neglect. Nevertheless as the student gains these data elsewhere the latter is the course we must select.

Briefly, then, if the appendix be studied in each case presenting itself at autopsy, what impresses us is the frequency with which we encounter indication of old inflammation, and this in cases which have afforded no history of acute abdominal disturbances. We encounter, that is, localized cicatrices causing narrowing and slight stenosis of the small organ. At other times, it is true, studying the organ removed for active disease, we find the mucosa unaffected save in the zone of acute inflammation, which generally is found in the distal half. There is thus apt to be either a series of mild inflammations of the mucosa unproductive of symptoms, or a first inflammatory attack so acute as to lead to grave results.

What in general is the nature of these attacks? Anatomically the appendix is a small edition of the bowel, resembling the colon in the absence of rugæ and villi, and the small intestine in that its longitudinal muscle forms a continuous sheet and is not gathered into bands; differing from both in the abundance of solitary lymph nodes in its submucosa. Over these the mucosa has a stretched appearance with few and short Lieberkühnian follicles, and, as Aschoff points out, the swelling caused by the presence of these nodes causes the outline of the lumen to be not circular but irregular. He regards the angles or depressions between contiguous nodes as the regions of election and

origin of the inflammatory process and affords figures from early cases which strongly support this view. Poynton and Paine have published experiments upon the rabbit, confirming the previous observations of Adrian that, under favorable conditions, the intravenous inoculation of sundry pathogenic organisms (pneumococcus, B. typhosus, diplococcus of acute rheumatism) sets up an acute localized appendicitis in the rabbit. This is of hematogenous origin and affects first the individual lymph nodes. These observations necessitate a renewed study of the earliest cases of the condition to determine whether serial sections of the human appendix demonstrate the existence of cases in which the lesion begins in the lymphoid tissue of the submucosa without evidence of preceding focal catarrh and necrosis of the mucosa.

We have long passed the period at which it was held that appendicitis originates from the presence of foreign bodies, pins, shot, etc., or of fecal concretions in the lumen of the organ. Where these are present undoubtedly they act as irritants favoring the development of local inflammation. So, too, the existence of constricting bands from old cicatrices by favoring the retention of fecal matter in the distal portion, favors the multiplication of putrefactive and other bacteria in the retained matter, and so seemingly predisposes to the supervention of catarrhal and graver inflammations. It must be admitted also that a relatively slight catarrh extending from the cæcum must tend toward closure of the proximal portion of the narrow tube, while similarly the very mobility of the tube favors its assuming abnormal positions and becoming temporarily kinked, again favoring retention of fecal contents in the distal portion and all its sequels. We cannot accept the view recently propounded by Metchnikoff that pin-worms and threadworms (oxyuris and trichocephalus) penetrating the mucosa are a dominant cause in setting up infection, while admitting that they are present in a small proportion of children exhibiting a milder form of catarrhal appendicitis. Briefly all these factors signify imperfect drainage.

By analogy with what we know regarding the earliest stages of infections involving the lymph nodes in the ileum, namely, typhoid and tuberculosis, we are inclined to the view that bacteria are conveyed into the submucous lymph nodes without there being necessarily any preliminary destruction of the surface epithelium. Wherever there is irritation from within the lumen, a simple catarrh is the first disturbance, with increase in goblet cells, congestion of the submucosa, and increased passage outward of wandering cells, and these cells, we believe, convey the bacteria into the underlying lymph nodes. Thus while hesitating to oppose the masterly studies of Aschoff, we are accustomed to conceive the process as affecting essentially the lymph nodes. It is the active proliferation of the cells in these nodes, and the consequent swelling with accompanying small-celled infiltration of the submucosa and muscularis that in our experience is the dominant feature in acute appendicitis. Further, as a result of the swelling, rather than as a normal condition, sharp angles or pits of the mucosa

become developed which clearly favor bacterial growth, necrosis, and ulceration of the mucosa. This we regard as a second, rather than as a first stage.

The condition apparently may proceed no farther than this and then become arrested, with little or no after-affects; or with the great swelling of one or more lymph nodes the overlying mucosa undergoes necrosis and removal, and with resolution a scar is produced with some constriction of the lumen (**simple catarrhal appendicitis.**)

Generally we observe more than this. It is a striking feature of the appendix, due possibly to its small size and poor drainage, that once set up, inflammation tends rapidly to involve all the coats. The limits of the affected lymph nodes become ill-defined, small round cells, lymphocytes, and polymorphs infiltrate the circular and longitudinal muscle layers, while the contents may become purulent (**purulent appendicitis**). Even the subserous vessels exhibit intense congestion, and at an early period there may be a peri-appendicitis with fibrin formation on the serous surface, long before there is any deep necrosis or sign of perforation. That this stage (**diffuse appendicitis**) is also recovered from is indicated by the frequency with which we encounter its after-effects, the so-called chronic appendicitis, seen where the appendix is removed after recurrent attacks, and characterized by diffuse fibrosis involving all the coats, and by the organized adhesions surrounding the organ. A long-continued process of fibrosis may lead to closure or obliteration of the lumen (**obliterative appendicitis**).

If the inflammation be more pronounced, the local toxic effects of the bacteria coupled with the inflammatory stasis, acting most powerfully in the region of primary invasion, lead to deep necrosis and ulceration which, extending through the outer coats, cause perforation (**perforative appendicitis**). Where the inflammation is more widespread and the stasis and necrosis affect the greater part of the distal portion, or even the appendix as a whole, widespread gangrene ensues (**gangrenous appendicitis**) and at operation little may be found save a detached slough lying in an abscess, or a more diffuse collection of foul serous fluid with admixture of fecal matter.

The further effects depend largely upon the position of the appendix, whether it pass down into the true pelvis, or be retroperitoneal, or pass upward along the outer aspect of the cecum and colon; depend upon the reactive power of the individual; depend also upon the nature of the infecting organism. Thus there may be a localized peri-appendical abscess well circumscribed, a spreading retroperitoneal inflammation, a diffuse peritonitis, an intense toxemia fatal before generalized peritonitis shows itself, a pylephlebitis extending along the veins of the appendix to the larger mesenteric veins and so to the portal vein, with multiple abscesses in the liver. The possibilities are manifold.

Colitis.—Colitis may be, as already stated, of very varied orders, namely, simple **catarrhal, follicular, membranous, ulcerative,** and others. Certain forms deserve additional notice. **Mucous colitis** is a remarkable

condition in which, from time to time, the individual passes casts of the colon formed almost entirely of mucus, which may be many inches in length; the condition may extend over many months and, after a period of quiescence, may recur. It is unaccompanied by any marked febrile reaction and it is doubtful whether it should be spoken of as inflammatory in nature, seeming rather to be of the nature of a secretory neurosis; the mucous glands being stimulated by the nervous mechanism of the bowel; it occurs most frequently in young women and those of neurotic temperament, and possibly it is associated with conditions of slight splanchnoptosis and congestion. It is recovered from by rest and improved body tone.

Fig. 307

Entameba. × 750. This shows the rather inconspicuous character of the living protozoan in the microscopic field. (From Bull. 1, 1913, Surgeon-General's Office.)

Of the specific inflammations of the colon two especially deserve note, namely, **amœbic colitis** and **epidemic bacillary colitis**. In amœbic colitis or dysentery the upper portion of the colon, viz., the cecum and ascending portion, is most involved, the characteristic feature being a marked thickening of the wall due in the main to a striking cellular infiltration of the submucosa, which on section stands out as a broad, pale, yellowish-white layer. Over this thickened area the mucous membrane is swollen and hyperemic, with a pronounced tendency to superficial necrosis and the formation of ulcers leading down into the swollen submucosa. In this way, large areas of the mucosa may disappear, leaving strands that bridge across the areas of ulceration. The ulcers rarely extend through the muscle coat and perforation is

rare. With healing there may be diffuse thickening of the bowel with papillary overgrowth of the remaining mucosa. Entamœbæ are to be found in considerable numbers in the infiltrated submucosa, which further contains abundant plasma cells. This form is largely tropical and subtropical, though cases have been described in persons who have never been in either zone.

Fig. 308
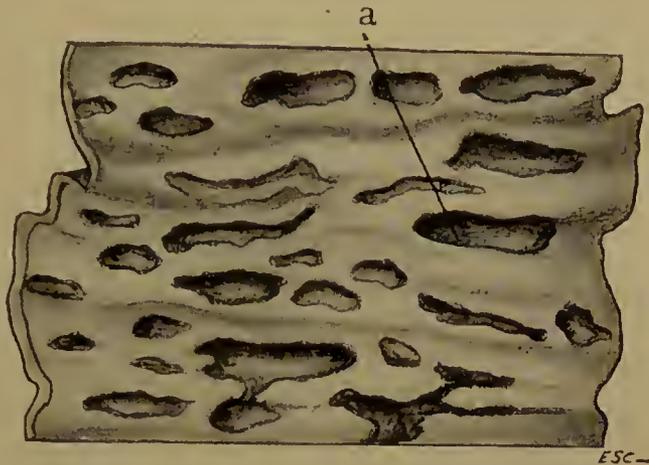
Ulcerative colitis, showing multiple, deep ulcers (*a*) mostly transverse. (McGill Path. Mus.)

Fig. 309
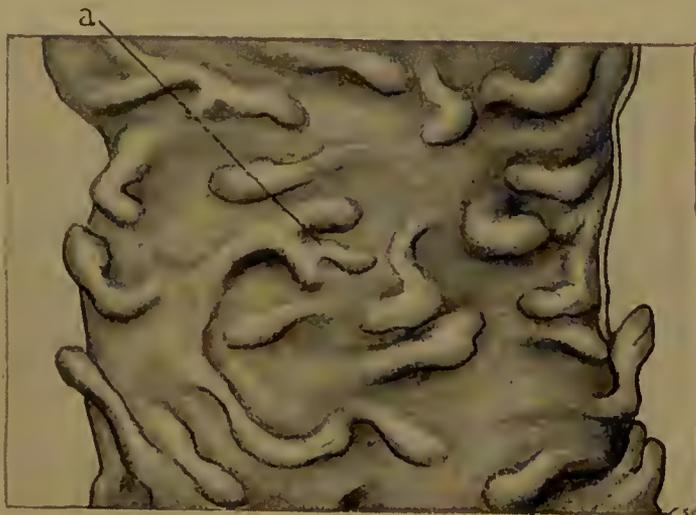
Colitis polyposa apparently secondary to old inflammation, showing at *a* an outstanding polyp. (McGill Path. Mus.)

Epidemic bacillary colitis (dysentery) shows some difference according to the strain of bacillus that is the causative agent. The more severe type is that found in the tropics and in Japan, due to Shiga's bacillus; this is strongly epidemic. In North America a somewhat milder form is encountered, particularly in inmates of asylums and other institutions, and in infants, causing one form of summer diarrhœa; this is due to the strain isolated by Flexner, as well as to allied forms. In these bacillary cases the rectum and sigmoid are as apt to be involved as are the upper reaches of the colon. There is intense congestion of the

mucosa with swelling and prominence of the rugæ and superficial necrosis of the mucosa leading to the formation of a membrane, and leading also to erosion and ulceration. These ulcers in the early stage are most apt to be along the ridges of the mucosa, while in severe cases, a purulent infiltration of the submucosa may ensue. The thickening of the submucosa is never so marked as in the amœbic form, nor is the bowel wall so greatly thickened. Both forms of colitis are characterized by dysentery which may be of long continuance.

Reference has already been made to **tuberculous colitis** and to the most characteristic form of proctitis, the so-called syphilitic.

Fig. 310

Section through intestine infected with trichina. (*a*) dilated follicle of Lieberkühn, showing transverse and oblique sections through an adult trichina; (*b*) follicles of Lieberkühn; (*d*) leukocytes in lymph channel; (*f*) submucosa infiltrated by leukocytes. (Romanovitch.)

Progressive Changes.—As already stated, **hypertrophy** of the bowel occurs above any region of chronic obstruction.

Tumors.—It may be said of the small intestine that primary tumors of any order are distinctly infrequent, and of the large intestine that benign tumors, save papillary growths, are rarely met. Nevertheless, cases are on record of various forms of benign tumors of the intestines, **fibroma, lipoma** (either subserous or submucous), **myoma** (ditto), **hemangioma,** and **lymphangioma.** Where these tumors project into the lumen of the bowel they may cause either obstruction or intussusception. **Papillomas,** whose epithelial portion is of the columnar type, are more common in the colon than in the small intestine and often are secondary to previous ulceration and continued inflammation (Fig. 301). They

may occur also in the rectum. Apart from growths immediately around the ampulla of Vater, the duodenum is singularly devoid of tumors.

FIG. 311
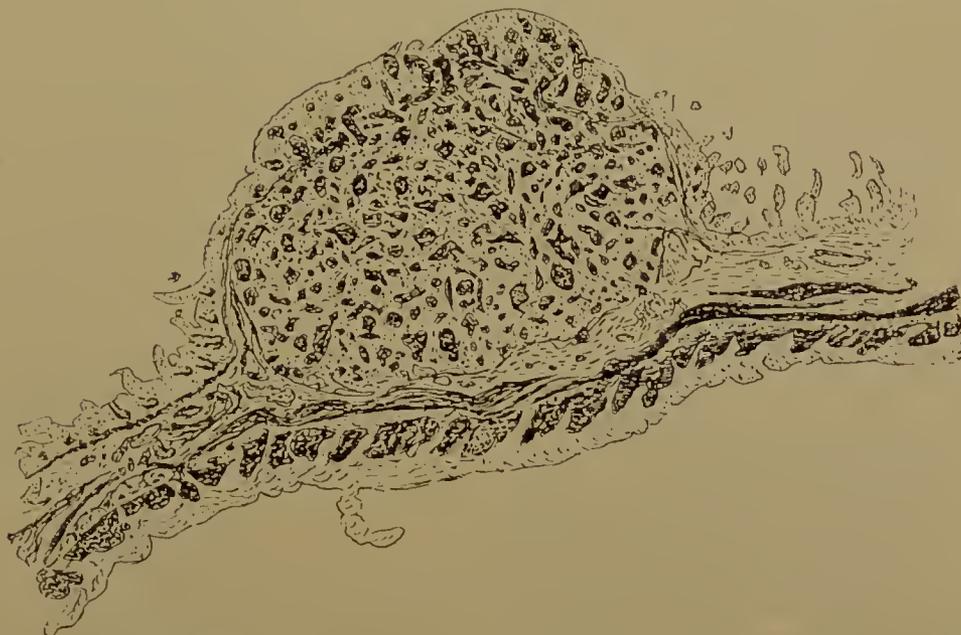
Diagram representing carcinoma of small intestine. The scattered masses of dark shading in the tumor are made up of carcinoma cells.

FIG. 312

Carcinoma of small intestine. (Magnification of Fig. 311.)

Of malignant growths, we encounter **carcinoma** in the duodenum in the region of the ampulla; it is very rare as a primary condition in the small intestine; it is more common in the colon, especially at the flexures, and still more common in the rectum. The next most frequent seat is at the lower end of the sigmoid. Of cancer in general, the rectum

42

comes fifth in the order of frequency of incidence. The forms that present themselves are, in the main, columnar-celled adenocarcinoma (see Fig. 192, p. 389), though we may also encounter more infiltrating forms, less adenocarcinomatous in character, with scirrhous tendencies, encircling and infiltrating broad areas of the bowel with accompanying contracture and narrowing of the lumen. Particularly in the rectum we meet with colloid cancer and, again, in the anal region, squamous epithelioma.

Fig. 313

Fig. 314

Carcinoma of large intestine. To the left a normal follicle of Lieberkühn. (Letulle.)

Carcinoma of appendix. (Schmorl.)

The last few years have afforded numerous examples of carcinoma of the distal portion of the appendix; the form is usually of the simplex or the scirrhous type, and what is very remarkable is that, with scarce an exception, the presence of the tumor has been a chance discovery, there being no symptoms, and what is more, little infiltration and no metastasis. The tumors in general have been small and well-defined. We have here, in short, the paradox of a "benign" carcinoma. It is worthy of note that the rare carcinomas of the lower end of the ileum are of the same benign type.

The result of carcinoma of the intestine is usually ulceration, which may pass on to perforation, but more frequently the growth is of the infiltrative type leading, both by its projection into the lumen and by the contraction of the gut, to stenosis and obstruction. Considerable hemorrhages are not so pronounced as in the case of gastric cancer.

Metastases are frequent in the retroperitoneal lymph nodes and on the peritoneum; the liver also is a frequent seat. Secondary carcinoma of the intestines is not common; cases are on record in which a primary cancer of the stomach has been followed by one or more solitary growths along the course of the intestine. There may further be infiltration by extension into the rectum of uterine carcinoma.

Primary **sarcoma** may occur as a round-celled growth originating generally in the submucosa, and this most frequently in the lower part of the ileum, though the rectum, cecum, and even the appendix furnish cases. Spindle-celled sarcoma is distinctly rare. **Lymphosarcoma** has the same regional distribution as has the round-celled sarcoma, and possibly they often fail to be distinguished one from the other. Secondary sarcomas occur in cases of generalized sarcomatosis; melanotic sarcomas particularly are apt to show themselves in the bowel wall.

THE PERITONEUM

Were it not for the necessity of peristalsis and motility of the stomach and intestines, the peritoneal cavity might be considered a superfluity. All those organs whose function demands a change of size and position are surrounded by a lubricated cavity in which to work, and of these cavities the peritoneal has by far the largest potential extent and actual surface. We must take it for granted that the student is familiar with the anatomy of the peritoneum, the disposition of the parietal portion, the nature of the mesenteries whereby the viscera hang relatively free within the cavity, and the relationship of these mesenteries to the blood supply, whereby, while the bowel is allowed a large measure of freedom and of variation in calibre, each part is prevented from escaping beyond a certain fixed distance from the origin of the mesenteric vessels. We must expect that the student is familiar also with the anatomy of the great omentum and its relationship to the stomach and the transverse colon respectively. The great addition to the superficies of the lining membrane of the peritoneal cavity afforded by the great omentum has for long attracted notice and numerous hypotheses have been suggested to explain its action. It is eminently vascular, its vessels being almost in contact with the contents of the peritoneum, so that if any portion of the omentum finds itself in an area of irritation, there is rapidly excited in it a secondary inflammatory process, and the ease with which it forms adhesions that are temporarily protective is very remarkable. With so large a free surface as that afforded by the peritoneum, it seems necessary to have some such protective organ to produce a rapid exudation of protective bodies; whether absorption occurs through it with the same freedom deserves further study. The general indications are that foreign particles present in the peritoneal cavity make their way with greatest freedom into the lymph spaces of the diaphragm.

The peritoneum is constituted by a layer of endothelial cells, which, while thin, are by no means inert, and rapidly react to any inflammation, undergoing swelling and often proliferation. These form a continuous membrane bounding the cavity save at two points, viz., the openings of the Fallopian tubes, through which there is a potential, though rarely actual, communication with the exterior. So, also, it must be remembered that over the ovaries the peritoneum becomes modified into a more cubical layer of cells, the germinal epithelium, from which by downgrowths originate the ovarian follicles. Beneath the endothelial layer is a subserous layer of loose connective tissue which in certain regions shows a pronounced tendency to undergo metaplasia into fat cells, as in the appendices epiploicæ, the mesenteries, and the omentum.

Abnormalities.—Of abnormalities, perhaps the one most frequently noticed is a variation in the length of the great omentum, which may vary from a small irregular fringe an inch in length to a massive apron often loaded with fat, a foot or more long. Similar variations are at times to be noted in the mesenteries, most marked in the case of organs which normally are incompletely surrounded by peritoneum, but may on occasion be found to possess mesenteries, *e. g.*, the cecum, and ascending colon, and even the kidney ("floating kidney"). We have already referred to abnormal length of the mesosigmoid as favoring the development of the condition of **megacolon** (**Hirschsprung's disease**).

Circulatory Disturbances.—The great vascularity of the peritoneum renders it most sensitive to circulatory disturbances; because it is thin the vessels are readily seen through it. Where there is **anemia** its pallor is marked; where there is **hyperemia**, active or passive, the injection is extreme.

Passive congestion is accompanied by pronounced transudation and production of ascites; even after death, transudation easily occurs, so that where immediately before death there has been a transfusion of saline solution, or after death an injection of embalming fluids, the peritoneal cavity may be found to contain a considerable amount of fluid which must not be mistaken for that of **ascites**. Apart from circulatory disturbances, it deserves note that the presence of ovarian tumors is frequently accompanied by a noticeable grade of ascites. The exact cause of this is somewhat obscure. On p. 421 we have already discussed ascites, and the related phenomena. How sensitive are the peritoneal vessels is well shown when the peritoneum is seen at operation even but a few minutes after a perforation of the bowel; there may be little obvious escape of bowel contents, yet the intestinal coils may be of the most angry, scarlet color. It will be understood from this that capillary subserous **hemorrhages** are not uncommon, especially where there has been some toxemia with degeneration of the capillary endothelium. A favorite seat for these hemorrhages seems to be the lower anterior half of the parietal peritoneum. They are seen particularly in severely toxic conditions, as well as in the hemorrhagic dis-

eases. Of gross hemorrhages into the peritoneal cavity the commonest and most extensive is that seen in ruptured tubal gestation, and in traumatic rupture of the liver, spleen, mesentery, and other organs. The effects of **thrombosis** and **embolism** upon the viscera are so grave that the accompanying changes in the peritoneum are relatively of minor importance, although they are of a like nature, viz., stasis, hemorrhage, and necrosis.

Inflammation.—Peritonitis.—Without attempting to make any full classification of the various acute inflammations of the peritoneum from a surgical standpoint, it may be laid down in the first place that three types are to be distinguished at autopsy: (1) **local circumscribed,** (2) **locally diffuse,** and (3) **universal.** We may find, that is, that by the rapid production of adhesions and the formation of fibrin an inflammation is sharply circumscribed to the region of primary disturbance. We may, for example, find an appendix bathed in pus which thus forms a peri-appendical abscess, and through omental adhesions and the fibrinous adhesions between surrounding coils of intestine, the rest of the peritoneal cavity wholly closed off from, and showing no signs of, the inflammatory process. Very often, however, we encounter an acute peritonitis of wider extent which fails to implicate some, it may be a considerable, part of the cavity, and this without the sharp line of demarcation by adhesions just noted. There may be, it is true, slight formation of fibrin between the coils at the periphery of the area, but so slight as to make it evident that some other factor, such as gravity, is likewise effective. This we term a **locally diffuse** peritonitis. For example, very frequently a pelvic peritonitis fails to extend into the middle area of the peritoneum, or a peritonitis involving the small intestines in general does not affect the area of the stomach and spleen. In the production of such a restricted inflammation, it is true that there are certain physical factors; thus, an inflammation may be largely restricted to the lesser peritoneal sac, or may be bounded by the mesentery or by the great omentum. The **universal** form is in general of a suppurative type, the pus being as abundant immediately beneath the diaphragm and around the spleen as in the pelvic cavity.

As regards the forms of peritonitis, it may be laid down that what is true of one serous sac is true of another. We meet, that is, **serous, serofibrinous, hemorrhagic,** and **purulent** forms, though the purulent forms are relatively more frequent than in the other serous cavities. It is not safe to imagine that these stand in their order of gravity, for the most quickly fatal case we have seen, one fatal within twelve hours after apparently perfect health, gave a serous fluid containing a pure culture of streptococci, while Bacillus coli infections may yield abundant foul pus and yet undergo complete recovery. What is particularly noticeable in this relationship is that typhoidal peritonitis is characterized by its diffuse character, absence of adhesions, and lack of pus cells; the danger of such a diminished reaction as is seen in cases of this nature lies in the rapid diffusion of the irritant, and generalization of the

process. Too few leukocytes exuded with defective fibrin formation on the one hand, and too abundant exudation of leukocytes on the other, with rapid digestion of fibrin as it is formed, equally favor a diffuse as distinct from a localized peritonitis. A form of purulent peritonitis that deserves mention is not infrequently seen following upon laparotomy, namely, that characterized by the presence of one or more isolated pockets of pus between the viscera. This occurs chiefly where drainage has been employed, the mere act of laparotomy having removed the greater part of the pus and thereby having improved the ability of the peritoneum to form adhesions; the very excellence of these adhesions prevents certain remote infected areas or pockets from obtaining free drainage, and in such pockets multiplication of bacteria with progressive pus formation may go on.

FIG. 315

a
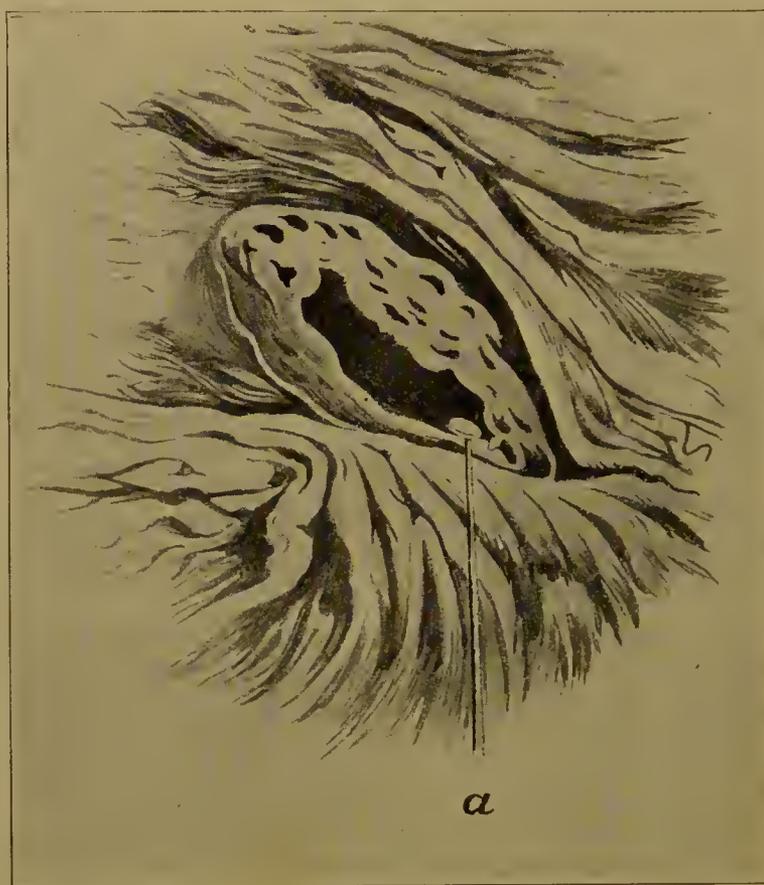
Exogenous perforation of the lower end of the ascending colon. The illustration, which is natural size, shows well the curious raised and perforated condition of the mucous membrane, seen from within the bowel, and at *a*, the opening through the muscle wall. (Adami.)

It is interesting to note how, in generalized peritonitis as in generalized pleurisy, the suppurative process rarely extends into the walls of the viscera and induces perforation; it is only where we have these localized areas of suppurative peritonitis that the presence of the pus upon a soft viscus arresting the nutrition of the walls of that viscus favors the production of what may be termed **exogenous ulceration** and perforation.

Etiology of Peritonitis.—As to the causes of peritonitis, these may be (1) **traumatic**, from without; (2) **enterogenous**; (3) from other viscera

by extension or by escape of contents, *e. g.*, bile and urine; (4) hematogenous, and (5) cryptogenous.

Of these the commonest are those originating from some portion of the bowel, either through rupture or perforation or secondary to inflammation of the same without actual rupture. It is a matter of every-day observation that a peri-appendicitis presents itself around an inflamed appendix, as if the peritoneum were preparing itself against the possible perforation. As to the bacterial causes, the forms most frequently found are the B. coli, streptococcus, staphylococcus, B. typhosus, pneumococcus, and gonococcus, the last particularly in pelvic peritonitis of the female. Where the contents of the bowel escape into the cavity, it is evident that one or more of a vast number of potentially pathogenic intestinal bacteria may be concerned. While the B. coli is most commonly encountered, many observers today regard this not as the primary but as a secondary pathogenic agent.

Chronic Peritonitis.—Where acute peritonitis undergoes resolution there is a great liability for adhesions to be left which undergo organization and often contracture, and these may be the cause of grave after-effects, viz., stricture, kinking, or internal hernia by a loop of bowel slipping under a fibrous band. This organization is a gradual process, and what is more, the irritation set up by displacement and consequent congestion of the viscera may itself constitute a cause of continuance of the process that cannot be designated otherwise than as a chronic peritonitis. Other forms of chronic peritonitis may be associated with long-continued passive congestion leading to a diffuse thickening of the peritoneum. A remarkable and extreme form of this chronic peritonitis is seen in the condition of **hyaloserositis**, or as it is termed, where it is local affecting particularly the surface of the liver, **icing liver**. In this condition a dense, porcelain-like deposit of hyaline tissue covers the surface of the liver and spleen and is accompanied by a thickening and contraction of the great omentum, leading to the formation of a thick hyaline mass lying along the transverse colon. More rarely the same condition is seen in the ileocecal region. Its exact causation is still undetermined, but in a certain proportion of

Fig. 316

Hyaloserositis of spleen; section through spleen showing at *a* an area of hyaloserositis of capsule; *b*, splenic tissue. (McGill Path. Mus.)

cases it is associated with a very chronic form of tuberculosis, and occasional caseous areas may be detected in the deposit. Coincidently, the pleuræ and pericardium are apt to present a similar condition. Accompanying this lesion, there is ascites.

Tuberculosis.—This is relatively common, and while at times it is dry, it is generally accompanied by a low form of serous peritonitis. Broadly two forms may be recognized: one in which the infection of the peritoneum is secondary to extension from one of the abdominal viscera, most often the intestine, although sometimes from the tube, ovary, or spleen; and the other a diffuse form in which no viscus appears to be primarily involved. What is the exact cause of this second form is debatable; certain cases appear clearly to be part and parcel of a hematogenous generalized tuberculosis. Others may be ascribed to the ulceration of a caseous lymph node into the cavity with dissemination of the bacilli over the surface of the peritoneum; there is a group of cases, however, resembling a parallel series confined to the pleura, in which the peritoneum appears to be a site of predilection and thus the condition seems to be primary, in the usual sense in which that term is employed.

The first of these forms presents itself as one or more localized patches of tubercles immediately above a tuberculous area in the viscus of origin. Such an area may be seen to extend continuously along the neighboring lymphatics, leading further to infection and adhesions of the serous surface of neighboring coils of the bowel. The condition generally is of rather chronic development associated with the formation of caseous conglomerate tubercles. In the early stage there is little exudation (**tuberculosis sicca**), but as the condition advances a serofibrinous peritonitis is liable to be set up.

The serous form is generalized; if seen in the early stage multiple miliary tubercles are scattered over any or all parts of the peritoneal surface, accompanied by a relatively acute serofibrinous, sometimes almost purulent peritonitis. In later stages, the tubercles may be seen as masses almost as large as a pea with universal adhesions between the bowel loops, and between omentum, intestines, and parietes. There is a striking liability for miliary peritoneal tuberculosis to complicate the late stages of the ascites due to portal cirrhosis of the liver.

Syphilis.—In strong contradistinction to tuberculosis, syphilis rarely induces peritoneal disturbances.

Actinomycosis.—Actinomycosis is liable to involve the peritoneum, secondary to its presence in the appendix or other region of the bowel. It may lead to fistulæ through the abdominal wall.

Abnormal Contents of the Peritoneum.—Apart from inflammatory exudates and blood, sundry foreign bodies may occasionally be encountered in the cavity. A subserous **fibroid** of the uterus may become snared off and be free in the cavity, as may also an **appendix epiploica**. Through rupture of the gall-bladder or common bile duct, not only **bile** but **gallstones** may gain entrance; as may also the **urine** from a ruptured bladder; in ectopic gestation, the fœtus may escape into the cavity, subsequently undergoing calcification (**lithopedion**); in attempted abortion, **needles** or other instruments may perforate the uterine wall and escape into the cavity; while during laparotomy, **sponges** and instruments have been inadvertently, and happily rarely, allowed to remain

in the cavity. In perforation of the intestines, besides the normal bowel contents, intestinal **worms** may occasionally be found to have reached the peritoneal sac.

FIG. 317
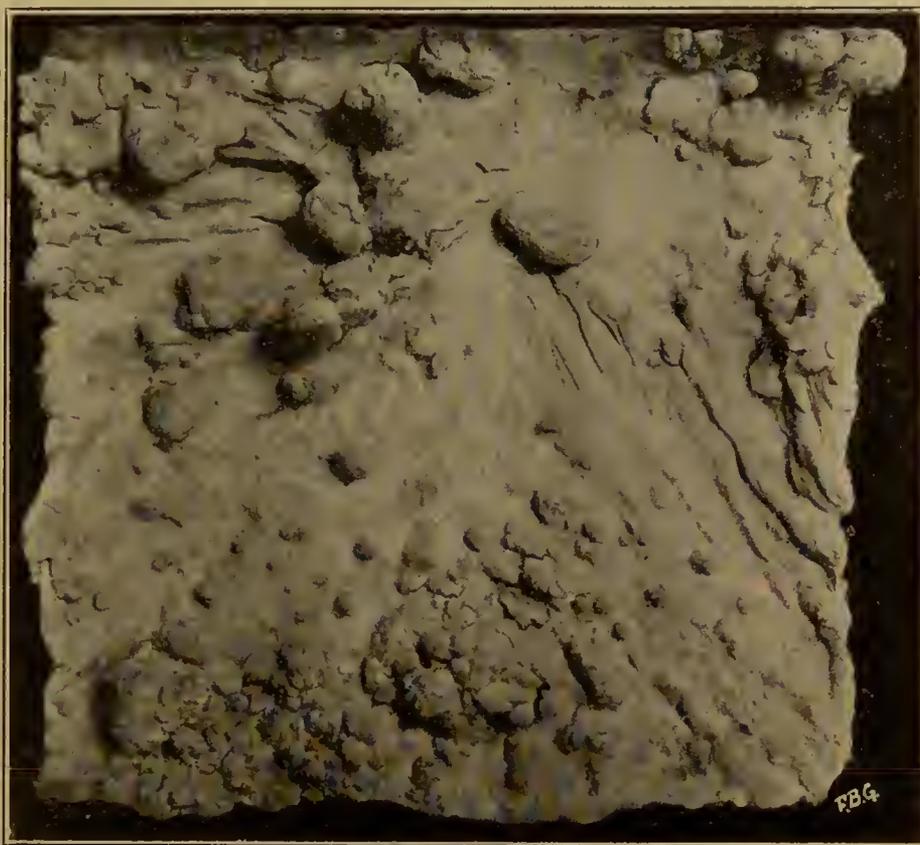
Tubercular peritonitis, infection by bovine type of organism, showing tubercles of all sizes lying on the thickened peritoneum. (McGill Pathological Museum.)

Regressive Changes.—Regressive changes in the peritoneum are inconsiderable. Occasionally we encounter necrosis with hemorrhage of an individual appendix epiploica through torsion of its peduncle. **Necrosis** of the peritoneum and subperitoneal fat occurs through the action of escaped pancreatic secretion. Small areas of **pigmentation** are occasionally observed, particularly in the pelvic region, possibly secondary to ecchymoses, although they appear to bear some relationship to chronic constipation; blood pigment may be observed long after a hemorrhage has been absorbed.

Progressive Changes. — What some authorities term **fibromas**, seen on the surface of the spleen in elderly individuals in the form of one or more flattened, tallow-like projec-

FIG. 318
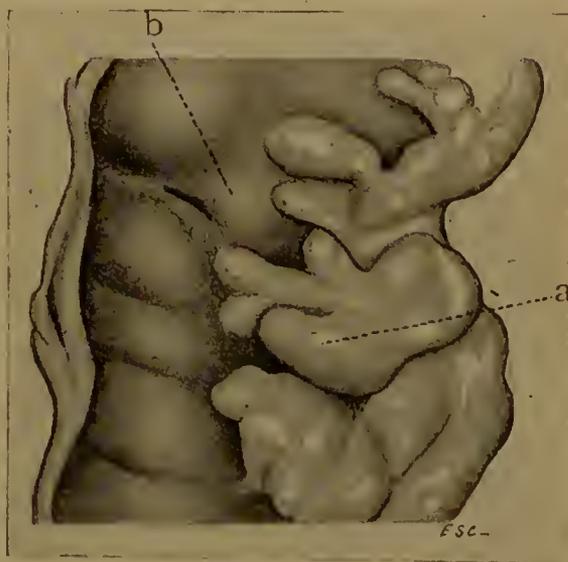
Fat necrosis of appendices epiploicæ, from a case of pancreatic necrosis ("hemorrhagic pancreatitis"): *a*, white areas of fat necrosis; *b*, colon. (McGill Path. Mus.)

tions, are not blastomatous but are allied to hyaloserositis. Of the peritoneum proper, namely, the endothelial membrane, there is but one new growth, the **endothelioma**, which at times closely resembles carcinoma in the finger-like processes that invade the underlying tissues. From the subperitoneal tissues, a series of connective-tissue tumors may develop, **lipoma**, **lipochondroma**, **lipoma myxomatodes**, **fibroma**, **angioma**, and **sarcoma**. These are particularly liable to grow in the root of the mesentery and in the retroperitoneal fat; especially in the fat overlying the kidneys are we liable to meet lipomatoid overgrowths and the production of massive tumors which may show myxomatous, chondromatous, osteomatous, and sarcomatous areas. **Teratomas** occasionally develop subperitoneally.

Secondary tumors are apt to involve the peritoneum by extension; thus the great omentum may be the seat of extensive carcinomatous growths in cases of carcinoma of the stomach, pancreas, gall-bladder, or ducts, and where there is colloid cancer of the rectum this spreads extensively along the peritoneum. Other secondary growths, notably **cystadenomas** of the ovary, grow by implantation, the rupture of one of the ovarian cysts liberating cells which may seed themselves upon the peritoneal surface, giving origin to very numerous small tumors. We have seen a similar diffuse implantation of **lymphosarcoma** over a large area of the peritoneum (Fig. 138, p. 335), which is also a favorite site for secondary melanotic growths.

Various orders of **cysts** may present themselves in connection with the peritoneum. As already noted, persistence of the median portion of the omphalomeseraic duct gives origin to a **vitello-intestinal** cyst. **Lymph cysts**, sometimes multiple, due to dilated, obstructed lymph vessels may be found, particularly in the mesenteries. **Parasitic cysts** may be encountered, due to rupture or escape of the contents in removal of a hydatid of the liver.

HERNIA

A hernia is the protrusion of any viscus or portion of the same through natural or accidental aperture in the parietes. In a secondary sense the term is also employed to include conditions in which a portion of the abdominal viscera passes, not through the parietes but through openings in the omentum, or the foramen of Winslow, or into peritoneal pockets. We thus make a distinction between the former, the **external**, and the latter, the **internal** hernias. Such protrusion may occur in regions of congenital weakness of the abdominal wall, as at the inguinal or femoral canals, the obturator foramen, the umbilicus, or, again, in regions of acquired weakness, as in the neighborhood of laparotomy scars, and in the middle line below the umbilicus, when, through pregnancy or other distending cause, the space between the recti muscles is enlarged. Weakness of the abdominal wall, with consequent giving-way owing to internal pressure, is the prime factor in the production of these external

hernias. With this giving-way a sac is formed, lined by the parietal peritoneum, and into that sac there may pass various viscera according to the situation of the sac, viz., the coils of the small intestine, masses of omentum, cecum and appendix or other portions of the large intestine and more rarely ovary, spleen, or portion of the stomach or urinary bladder, liver, etc. As the sac enlarges it is apt to expand and in this way to present a relatively narrow neck with a more voluminous extra-abdominal cavity. This patency of the sac may continue, and reduction of the contents of the sac may occur, or be induced (**reducible hernia**). But through expansion of the contents of the bowel in the sac, congestion may be set up with resultant adhesions, or the very bulk of the tissue passing in may oppose return. It is in these conditions that there is imminent danger; with such **incarceration** the relative constriction of the neck obstructs the free return of venous blood. The hernial mass becomes larger through this congestion, the constriction, therefore, more pronounced, and a progressive enlargement is the result which, ending in stasis, leads to necrosis and gangrene of the hernial contents, and these, whenever any portion of the bowel containing feces is concerned, eventually become putrefactive and gangrenous.

1. **External Hernias.**—The following forms are to be recognized: **Inguinal Hernia.**—In man this is the commonest form, and it is also seen in woman. It is due to undue patency or weakness of the tissues in the region of the inguinal canal. Thus viscera may pass down the inguinal canal itself (**oblique inguinal hernia**) or the external abdominal ring being unduly large and the parietes over it being weak, there is developed what is known as **direct inguinal hernia**, originating internally to the inner side of the internal orifice of the canal but presenting itself through the external ring. Either of these forms may now extend down the scrotum to form a **scrotal hernia**. If the hernia does not extend through the external ring we have what is known as **incomplete inguinal hernia.**

2. **Femoral Hernia.**—This is more common in woman, the channel being formed along the course of the femoral vessels and so below Poupart's ligament and along the upper part of Hunter's canal.

3. **Umbilical Hernia.**—Abdominal contents may protrude through the umbilical ring. This may be congenital but it is most often seen in the multiparous female; the sac may attain great size. Somewhat similar to this, but occurring below the navel in the middle line is the **abdominal hernia**. This often occurs in women who have borne children, or as the result of a laparotomy in the median line. **Epigastric abdominal hernia** in the middle line above the navel is rare.

4. **Other Forms.**—Other forms are also rare, viz., **obturator hernia**, through the obturator foramen; **sciatic**, through the sacrosciatic notch; **perineal**, through the levator ani; **vaginal**, through the giving way of the wall of Douglas' pouch. **Diaphragmatic hernia** may be due either to a congenital deficiency in the formation of the diaphragm, nearly always on the left side, as a result of which, stomach, spleen, kidney, and loops

of intestine may be found occupying the thorax; or it may be acquired through traumatic rupture.

Internal Hernias.—Internal hernias show no protrusion through the abdominal parietes; they are relatively infrequent. Through rupture or imperfect formation of the mesentery occasionally the abdominal contents become retroperitoneal and a large, if not the greater, portion of the intestine, may pass behind some part of the peritoneum; or, again, loops of the intestine may be pressed through the foramen of Winslow, to the filling of the lesser omental sac. The fossa duodenalis may further give way; similarly the subcecal and intersigmoid fossæ may form sacs containing hernial masses of the intestine.

THE LIVER

Simple as is the structure of the liver, there is no organ in the body to which more various metabolic activities have been justly attributed. Its great importance is indicated by its size (1400 to 1600 grams). It is the main organ for the removal of products of broken-down erythrocytes: the separation of the iron of the hemoglobin from the discharged iron-free bile pigment: the discharge of the bile-salts and of cholesterin: the regulation of the sugar supply of the blood and tissues in general, through its glycogenic activities: the regulation similarly, of the circulating fats, and storage of the same and other lipoids: the formation of urea. Situated at the head of the portal system, which brings to it the various substances absorbed from the walls of the intestine, the liver acts as a protective organ, arresting and excreting or destroying toxic bodies of various orders, and in this way accumulating certain poisons such as arsenic and phosphorus. As with the organs in general, although capable of withstanding insults of particular orders in particular degrees, and although intended for such a purpose, nevertheless these insults may at times be extreme and the liver may thereby suffer. It is, therefore, the seat of many inflammatory and degenerative processes, which, in time, interfere with its prime metabolic purposes; hence the far-reaching importance of pathological change in its structure, and the profound general disturbances to which disease of this viscus may give rise. Space forbids that we should here enter into the minute anatomy, which should be known to every student of histology. At most, we may recall that it is abundantly vascular, so vascular as to be able to contain the whole blood supply of the body; that it has a double blood supply, systemic and arterial through the hepatic artery, portal and venous through the portal vein; that the entering blood reaches the individual lobules from their periphery to be collected into a central, intralobular branch of the hepatic vein, which carries it to the inferior vena cava. Contrariwise, the bile capillaries pass outward to the periphery of the lobule, there joining to form the bile ducts, and thus each individual liver cell is in immediate apposition, on at least one

aspect, to a blood capillary or sinusoid and, on another, to a bile capillary. There is, indeed, evidence that within the individual liver cell there are fine channels intimately connected with both systems.

Abnormalities.—The abnormalities of the liver, as compared with other organs of the body, are distinctly few. It may show considerable **variation in shape;** one lobe, especially the left, may be abnormally small, or there may be **accessory lobes,** in general small, or masses, snared off in the course of development, may lie in the neighborhood of the main organ, *e. g.*, in the suspensory ligament or the great omentum. **Liebermeister's grooves,** depressions running in the anteroposterior direction, while most often acquired, may be congenital; in all cases they appear to be due to an irregular development or an hypertrophy of the diaphragmatic musculature, the grooves corresponding to regions of pressure of the muscle bands upon the upper surface of the liver. There may further be variations in the position of the portal vein and a few cases are on record in which there has been inclusion of adrenal tissue.

FIG. 319
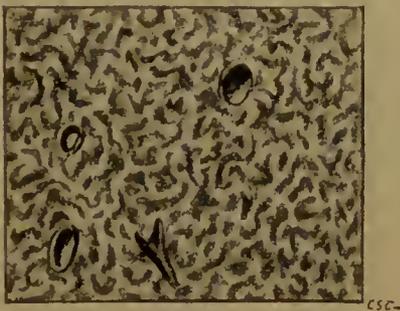
FIG. 320

Nutmeg liver, showing a small area, natural size, of the cut surface. (McGill Path. Mus.)
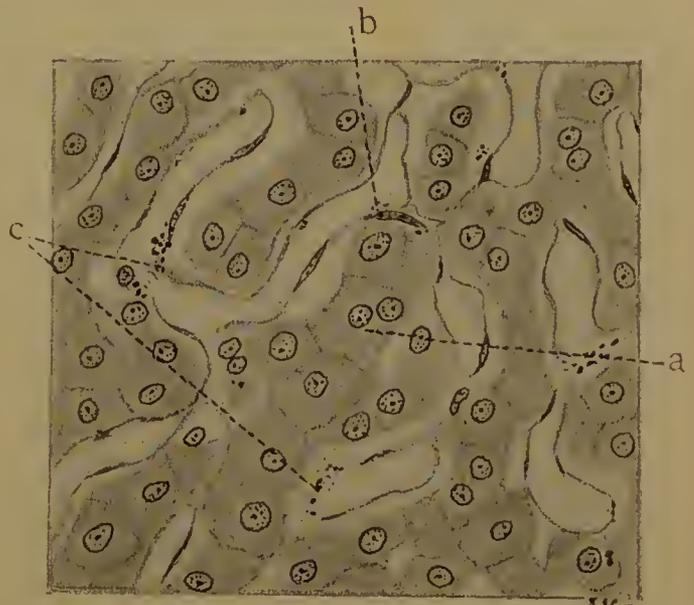
Early stage of passive congestion of liver from near centre of lobule, showing *a*, liver cells, somewhat shrunken; *b*, wall of capillary, separated from liver cells by œdematous fluid; *c*, pigment from destroyed red blood corpuscles. The corpuscles have been left out of the drawing for the sake of clearness.

Circulatory Disturbances.—The liver participates in general **anemia,** and then is found pale, small and flabby, with sharp edges. Local pressure may produce local anemia. **Active hyperemia,** or more accurately active portal congestion, may be physiological, as after a hearty meal, and possibly is the cause of the large liver of the tropical dweller, whose diet is in excess of the requirements of the climate. In infective and toxic states the cloudy swelling to be presently noted is an accompaniment of active congestion. In temperate zones, **passive congestion**

is much more commonly encountered as a result of chronic obstructive heart or liver disease. The organ is enlarged, tense, its edges more than usually obtuse, its color from a chocolate brown to a dark purple; often, also, with enlargement of the right side of the heart and of the liver, there is to be noted a distinct hollowing of the upper aspect of the left lobe—a cardiac gulf or groove. Where the condition has been long continued, the surface is apt to be obscurely granular, due to the fibrosis which inevitably follows long-continued moderate congestion. On section of a moderately early case the appearance is characteristic, and gives the name "nutmeg liver" to this condition; the centres of the lobules are dark red from congestion, a congestion so extreme that

Fig. 321

Fig. 322
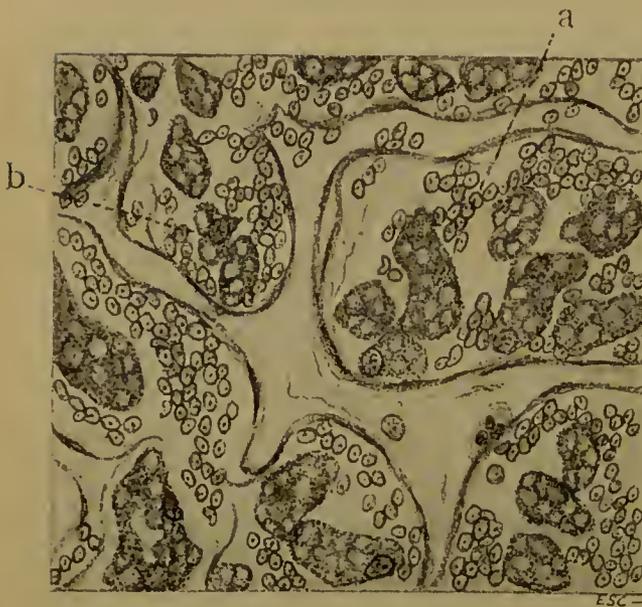
Later stage of the same: *a*, red blood corpuscles which have escaped into the space previously occupied by the liver cells; *b*, greatly shrunken and degenerated liver cells. The sinusoids are even more dilated than in the earlier stage. (After Mallory.)
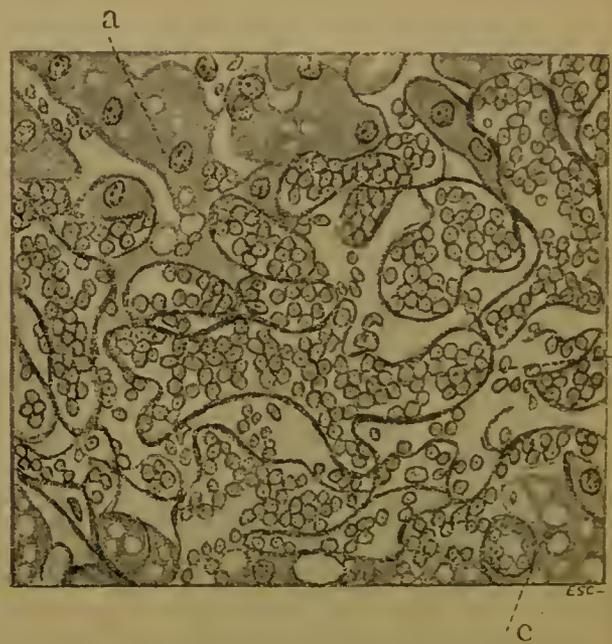
Still later stage of the same condition. Here the cells of the mid-zone of the lobule have completely disappeared, their place being taken by extravasated blood corpuscles (*b*); *a*, remaining cells of the peripheral zone of the lobule; *c*, cells of inner zone showing abundant fatty vacuoles. (After Mallory.)

the cells of the central zone of the lobule undergo atrophy; owing to the obstruction to the circulation, the fat brought by the portal blood is not actively consumed and is stored up in the remaining peripheral part of the lobule, the light color of which contrasts strongly with the red or brown centre; the cut surface of the liver tissue resembles very closely the grated surface of the nutmeg of domesticity. As the congestion continues, both the lack of nourishment, owing to the slowed circulation, and the increased venous pressure lead to an extending atrophy of the cells of the centres of the lobules and with this there is some increase of the connective tissue around the central vein; with the continued malnutrition of the peripheral cells less fat is stored up, the whole organ thus assum-

ing a darker color with some shrinkage and increased firmness —**cyanotic induration**. Congestion secondary to thrombosis of the hepatic vein or its obliteration is rare.

Infarcts of the liver are of two kinds, the anemic or white, and the red. These have a different origin; the **white infarct** is brought about by embolic or other closure of a branch of the hepatic artery. Despite the relatively small size of the hepatic artery as compared with the portal vein, its experimental closure leads to a necrosis of the organ or, stated otherwise, arterial blood is necessary for the perfect nutrition of the liver. Thus, despite continued portal circulation, if a branch of the hepatic artery be obliterated, *especially where there is already an impaired general circulation*, the local area of supply undergoes necrosis, becomes pale, and shows typical white infarct formation. **Red infarct** is the result of closure by embolism or thrombosis of a branch of the portal vein. The appearance obtained is that of a sharply defined,

Fig. 323

Red infarct of liver. Section of the organ (less than the natural size), so cut as to expose two branches of the portal vein into which extends a thrombus (*b*); *a*, area of red infarct. (McGill Path. Mus.)

more or less wedge-shaped area of darker red color standing out in sharp contrast to the paler brown liver tissue. If necrosis be taken as the essential property of an infarct, this is no true infarct. Sections studied under the microscope show the cells still intact with well-staining nuclei, but each column of liver cells is surrounded by intensely dilated and congested sinusoids or capillaries. The condition, however, may be compared with the red infarct of the lung, where similarly there is a double circulation, and where closure of a branch of the pulmonary artery is followed by an intense congestion without necrosis of the involved tissue. The liver is a favorite site for minute cell **emboli**, either those derived from the placenta, or in rarer cases from the bone marrow, or from peritoneal or other fat cells after operation, or from conglutinated erythrocytes. They cause **focal necroses**.

Thrombosis of the main trunk of the portal vein, again resembling that of the main pulmonary artery, is unaccompanied by this infarct formation or by any marked change in the liver tissue, save when the thrombosis is of infective nature. Thrombosis of this vein is not uncommon, and may be brought about in more than one way. The commonest cause is by extension of thrombosis or thrombophlebitis in one of the mesenteric or other branches of the portal vein, from an area of inflammation or an operative lesion; or inflammation within the liver, by affecting the wall of one of the larger branches may cause

a localized thrombosis within it, which may extend and involve still larger branches.

Hemorrhage is most commonly traumatic, but small hemorrhages may occur around actively growing tumors, in the neighborhood of abscesses, in cases of the so-called hemorrhagic diseases, in eclampsia, and in "acute yellow atrophy."

A condition not often recognized is that of **œdema** of the liver. Our attention was first drawn to this in the routine insertion of pipettes to obtain liver juice for bacteriological purposes, when not infrequently we obtained a fluid that was thin and evidently a mixture of serum with blood. Microscopic section of livers affording such fluid presents a characteristic picture. The columns of liver cells appear shrunken and widely separated, and on examining the space between the columns the capillary channels are seen separated from the liver cells by clear spaces, evidently containing serous fluid (see Fig. 321). In some cases, the accompanying atrophy of the liver cells appears to be primary, in which case the œdema is evidently *ex vacuo*.

Inflammation.—Acute Hepatitis.—It is perhaps difficult to make anything like a sharp line of demarcation between the active physiological hyperemia to which we have already referred and what is known as acute hepatitis. In both conditions the organ is enlarged and hyperemic, but where toxic agents such as the toxins of acute infections and certain mineral poisons, etc., or again the products of abnormal digestion are brought to the organ, it is common to find cellular changes in addition to the hyperemia, and it is this cloudy, passing on to fatty, degeneration that is regarded as the distinguishing feature of general inflammation of the organ. In the severer cases there is in addition a certain amount of small-celled infiltration along the interlobular portal sheaths. There is the same doubt here, as in acute nephritis, as to whether these cellular changes should be regarded as inflammatory or as pure degenerations. Certain it is, that extreme toxic action leads to cell degeneration, acute atrophy, and necrosis. In what is known as **acute red atrophy** we have a combination of intense congestion with "jumbling" and shrinkage of the cells, and even more pronounced conditions are seen in **acute yellow atrophy** in which the necrotic changes accompanying the acute atrophy are still more marked. We mention these here because, by some observers at least, acute red atrophy is held to precede one form of cirrhosis or chronic hepatitis.

In addition to this so-called simple diffuse hepatitis we not infrequently encounter a more sporadic **suppurative hepatitis**; this may be in two forms, presenting itself either in the form of multiple small abscesses or of a few or a solitary large abscess. The multiple abscesses may have either (a) a hematogenous or (b) a biliary origin. The former is perhaps the commoner. Where there is suppurative inflammation of the appendix or intestinal tract, a local purulent thrombophlebitis may be followed by loosening of the infective material in some branch of the mesenteric veins with formation of multiple infective emboli

in the small hepatic branches of the portal vein. Each embolus of this nature may then become the centre of a small abscess, and these may be so abundant as to be strung together along the course of a group of vessel branches, like a bunch of small grapes (**pylephlebitic abscesses**). Surrounding these there is intense congestion of the hepatic parenchyma. But, similarly, an acute ascending infection along the intrahepatic bile ducts, secondary often to suppurative cholecystitis, may lead to a very similar appearance, though here the angry and somewhat dilated appearance of the larger bile ducts and the presence of pus within them gives a clue to the origin of the abscesses.

FIG. 324
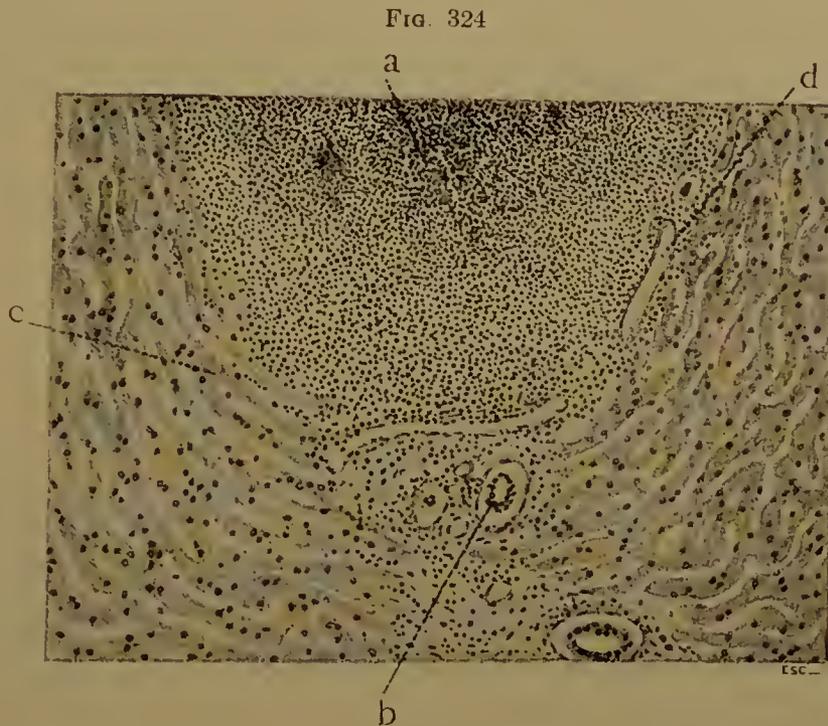
Section through a small abscess of liver from a case of pylephlebitis: *a*, abscess; *b*, dilated bile duct with epithelium loosened from its basement membrane; *c*, surrounding liver cells compressed by the abscess; *d*, compressed veins.

The large **tropical abscess,** or abscesses of the liver have a wholly different origin. These are found most often in the dome of the liver and may be several inches in diameter. They contain a thick, broken-down fluid material the color of chocolat au lait, composed of necrotic liver tissue with moderately abundant leukocytes; they have somewhat ragged boundaries formed of necrosing liver tissue, and with their extension may rupture through the diaphragm into the lung tissue or bronchi, or, again, into the peritoneal cavity. These are **amœbic abscesses,** and are secondary to amœbic colitis (dysentery). Careful examination of the boundary tissue of these abscesses reveals abundant entamœbæ, which, according to our experience may be found still active and motile on a warm stage twelve hours and more after the death of the subject. How these entamœbæ gain entrance to the liver is perhaps debatable; the central position of the abscess suggests that they have gained entrance by the portal blood.

43

Chronic Inflammation.—Cirrhoses and Specific Inflammations.—By the term cirrhosis we imply a diffuse extensive laying-down of fibrous tissue within the liver. Saying this, it will be seen that anatomically such deposit of fibrous tissue may have various origins. It may originate around the branches of the portal vein or may be of the nature of a chronic periarteritis around the branches of the hepatic artery; it may show itself particularly in connection with the intralobular branches of the hepatic vein or be secondary to an inflammation and irritation of the bile ducts. It may be an extension inward of a chronic inflammation affecting Glisson's capsule, or lastly, as in syphilis and tuberculosis, it may be the outcome of focal specific tubercular changes so abundant as to be generalized. Anatomically, therefore, we may expect to find numerous types of cirrhosis; as a matter of fact the arterial form is almost unknown, that in connection with the hepatic veins, while seen in chronic congestion, is but of slight degree, and that following a chronic inflammation of the capsule is also so rare as to be negligible. The important forms to recognize are the **portal,** the **biliary,** and the **diffuse syphilitic.**

FIG. 325
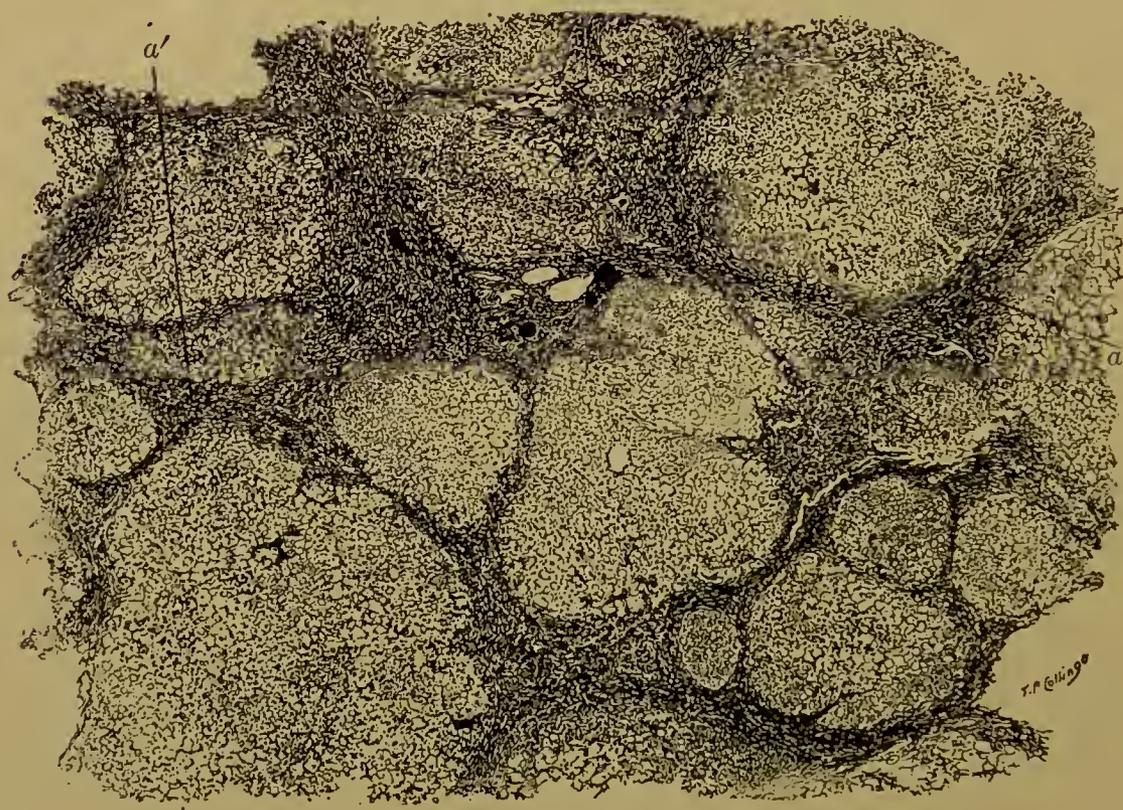
Portal cirrhosis of the liver: *a, a′*, tracts of fibrous tissue enclosing masses of fatty liver-cells. The distinction between the different lobules and the radiating arrangements of the cells is entirely ost. (Green.)

Laennec's Cirrhosis or **Portal Cirrhosis** (inaccurately termed atrophic cirrhosis).—This is the commonest type of cirrhotic change. It is found frequently in those addicted to alcohol, hence the term **gin-drinker's liver,** but may occur among native Hindoos and children who have never known spirituous liquor. Clinically it is characterized

by dyspepsia and anorexia, ascites more frequently than jaundice, progressive emaciation and weakness, a slight grade of anemia, a fair enlargement of the spleen, and death either from intercurrent tuberculosis or inflammation of the lungs, or sometimes œsophageal hemorrhage. Studying the course of the disease, if recognized early, the liver is found greatly enlarged, but in the course of months it is apt to undergo progressive shrinkage until in a certain proportion of cases it is very much smaller than normal. According to our experience, in general the liver in this condition is larger and heavier than normal. The main features of the organ at autopsy are the nodular surface (**hobnail liver**) the extreme firmness on section, due to the increased fibrosis, and usually the distinctly yellow color of the cut organ. It was this last feature that primarily gave the name (*κιῤῥός*, yellow) to the condition, although by association we now apply this term to any condition of diffuse fibrosis. On inspection of the cut surface the liver parenchyma is seen to be separated off into small islands or irregular lobules by bands of fibrous tissue. Under the microscope in typical cases what is characteristic is that the broad

FIG. 326

Hobnailed liver with small hobnails, natural size. (McGill Path. Mus.)

but irregular bands of dense fibrous tissue are sharply defined from these islands of parenchyma, nor are these islands seen to be well-formed lobules. On the contrary, individual islands appear to be formed of clusters of several imperfect lobules (imperfect because

FIG. 327

Hobnailed liver with large hobnails due to regeneration of the parenchyma, natural size. (McGill Path. Mus.)

FIG. 328
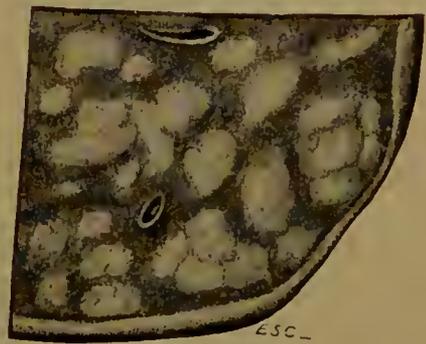
Portion of the same seen on section.

their intralobular veins are not, in general, central). It is this formation that gives the additional name of **multilobular cirrhosis** to this particular type. Further, the bands present relatively few included bile ducts. Especially in the young, a variant of this type

is seen in which many of the nodules are relatively large (Figs. 328, 329), much larger than hobnails; a study of them shows that here we deal with a regenerative process. From this simple regeneration we may pass on, particularly in adults, to cirrhosis with multiple adenomatous nodules and cirrhosis with accompanying diffuse carcinomatosis.

The cause of this hobnail appearance is obvious; it is the old story of eventual contraction of newly formed connective tissue with resultant projection of the intermediate masses.

Fig. 329
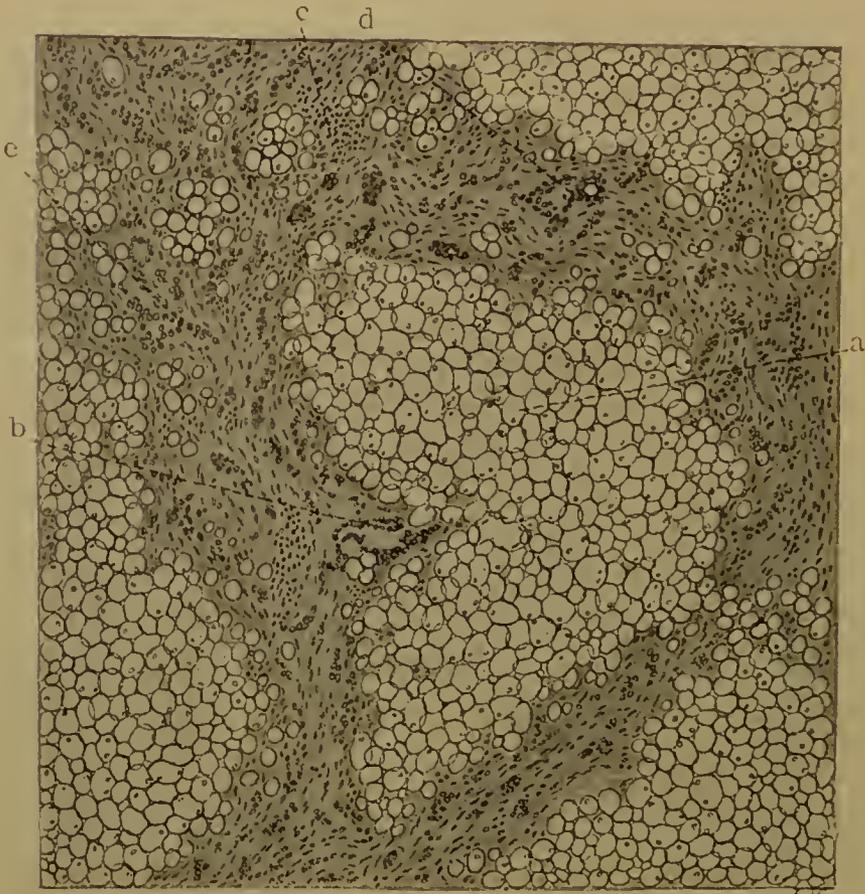
Section from a liver enlarged and showing combined extreme fatty infiltration and moderate cirrhosis, approximating histologically more to Hanot's than to Laennec's type: *a*, fattily infiltrated liver cells; *b* and *d*, bile ducts, increased in number; *c*, round-celled infiltration of fibrous tissue.

As to the cause of "portal" cirrhosis, there has been great debate. The commonest type of alcoholic liver is that of advanced fatty infiltration. In such livers we notice often that the portal sheaths show a small-celled infiltration or slight fibrosis. It is presumed that some irritant agent, brought by the portal blood, sets up a low form of irritation around the branches generally, as also that the same irritant leads to degeneration and atrophy of those liver cells which are exposed to the main brunt of the toxic agent, that thus there is a coincident periportal growth of connective tissue and destruction of the peripheral cells of the lobules, the resultant irregular breadth of the bands of fibrous tissue being dependent upon the irregular distribution of the portal

branches around the lobules. As to the nature of the irritant, it has been found that alcohol alone administered to the lower animals will not set up cirrhosis, and that acute atrophy, pure and simple, of liver cells, such as is produced by chloroform, is followed not by cirrhosis but by regeneration from the undestroyed liver cells. Hektoen, Weaver, and others have occasionally noted that inoculation of laboratory animals with certain strains of B. coli will set up the condition, but this with no constancy. Recently, Opie has shown that if, after preliminary necrosis of the liver cells by means of chloroform, the organ be subjected to infection by a mild strain of B. coli or its toxins, then constantly a cirrhotic process is developed. This, it is true, is not a pure portal cirrhosis, because chloroform tends to produce a central rather than a peripheral necrosis. Indeed from the similarity of the histological picture produced thus following upon a centrilobular necrosis, to that seen in the common human multilobular type, it may be questioned whether the loss of liver parenchyma in the latter is primarily or essentially peripheral and whether we are right in speaking of this as portal cirrhosis. But these observations strongly support our contention that there are two factors at work in the production of cirrhosis, viz., in the first place an agent acting through the stomach and intestines and there setting up conditions which favor subinfection (see p. 144), and in the second place, in consequence of the gastro-enteritis, the undue passage into the portal system of organisms of the B. coli type through the damaged mucosa.

We have here described the typical form of portal cirrhosis; it must, however, be borne in mind that the typical case is the exception and not the rule. In a large number of cases this very growth of fibrous tissue within the liver leads to grave disturbance of the biliary system and so to the intercurrent development of jaundice and coincident irritation of the bile ducts. Further, quite a large proportion of cases of cirrhosis exhibit a brownish pigmentation both of the liver cells and of the fibrous tissue, the pigment being iron-containing. There is evidently in these cases some hemolytic agent at work with excessive liberation of hemoglobin. The most advanced cases of this nature show a generalized pigmentation and constitute the condition of **hemochromatosis**. Often in these there is accompanying fibrosis and atrophy of the pancreas (**bronzed diabetes**). The ascites and enlarged spleen in portal cirrhosis appear clearly to be associated with the contraction of the fibrous tissue and accompanying compression of the intrahepatic portal vessels, leading to obstruction.

While making this statement, mention must be made of a remarkable condition known as **Banti's disease**, or, according to Banti himself, **hemolytic splenomegaly**. Here, enlargement of the spleen is the first disturbance noted, and after the course of some years this is followed by portal cirrhosis of the liver. Banti's observations on the result of ablation of the spleen indicate that the overgrown spleen functionates in excess, the anemia sometimes ceasing when the organ is

removed; presumably, it is the products of excessive hemolysis that act as the portal irritant.

Biliary Cirrhosis.—Of this we recognize two forms, the **obstructive** and what is known as **Hanot's** or **hypertrophic cirrhosis**. We confess that we have never met with an example that we could surely say was of this second kind, and the condition seems to be very rare in North America, although numerous cases have been reported, particularly in French literature.

The obstructive form of biliary cirrhosis is to be encountered where from one cause or another there is continued obstruction in, or complete stenosis of, the common bile duct. It is to be seen, for example, in infants presenting congenital atresia or absence of the duct, or where there has been long-continued impaction of gallstones, or pressure upon the duct from without or where there is occlusion by tumors growing within the duct. In all these cases the liver is enlarged and shows extreme jaundice, as do the other tissues of the body. All the bile ducts throughout it are markedly dilated and around each is a broad zone of new connective tissue in which, in part through dilatation, in part through cellular proliferation, a chaplet or circle of terminal bile ducts stands out prominently. Here clearly is a cirrhosis around the bile passages, which may well be compared with the fibrosis around the branches of the pancreatic duct following obstruction of the same. In both cases the reabsorption of the excreted fluid appears to be the primary irritant. In our laboratory Ford collected a considerable number of such cases.

Hanot's Cirrhosis.—In this we have a train of symptoms widely different from those of ordinary portal cirrhosis. There is not so marked gastro-intestinal disturbance; there is little tendency to ascites, but what is most marked is a succession of moderately acute attacks of jaundice, and after each attack the liver is found larger, the jaundice takes a longer and longer time to pass off, until it becomes continuous and the liver attains an enormous size. At autopsy, there is total absence of hobnailing, the organ is greatly jaundiced, cuts firmly, and under the microscope the fibrosis is much more evenly distributed. Around individual lobules (**monolobular cirrhosis**) the bands are not so sharply defined and exhibit numerous bile ducts, or more accurately pseudo-bile ducts, little worm-like, convoluted masses of cells having no regular lumen and appearing to represent, many of them, collections of shrunken liver cells snared off and compressed by the connective tissue as it advances into the lobule. This appearance is not entirely confined to Hanot's cirrhosis, and is well seen in Fig. 331. In other words, some cases of what appear to be ordinary cirrhosis show here and there similar appearances; as we have said, a large proportion of cases of cirrhosis are apt to become secondarily of mixed type.

The prominence of the icteric manifestations in Hanot's cirrhosis suggests strongly that here the irritation is of biliary origin. It has been suggested that it is due to an ascending chronic inflammation

of the finer bile ducts, and that it is of infective origin, but this has still to be surely determined.

Fig. 330
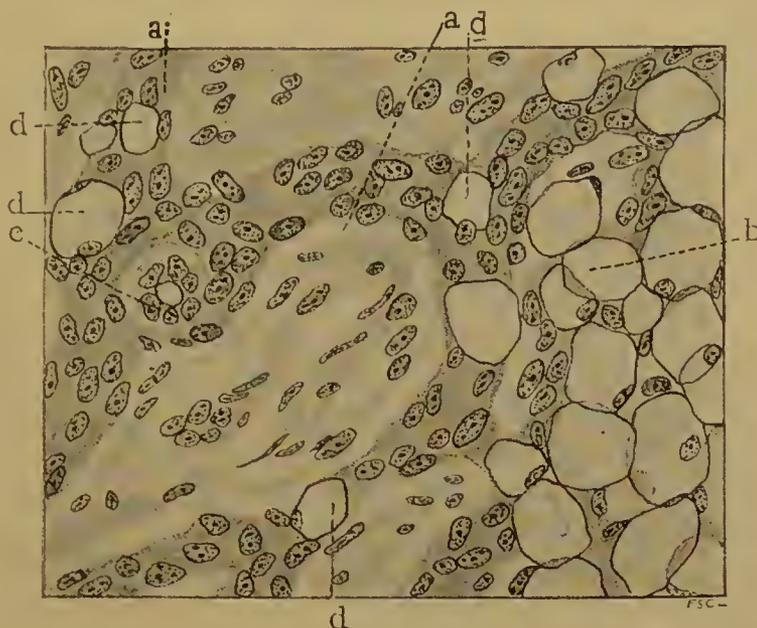
Section from a liver under high magnification demonstrating reversionary metamorphosis of the liver cells at the periphery of a lobule under the influence of the surrounding fibrosis, into small cells approximating to the bile-duct type, though unprovided with a lumen: *a*, reduced liver cells forming a pseudo-bile-duct; *b*, liver cells of lobule with extreme fatty infiltration; *c*, bile duct proper; *d*, cells of pseudo-bile-duct still containing fat, showing thus their liver-cell origin.

Syphilitic Cirrhosis.—In a syphilitic stillborn infant one of the most striking features is the abundance of spirochetes in the liver tissue; in infants showing syphilitic manifestations the organ is apt to be of relatively great size, and to present on microscopic examination abundant, small-celled infiltration in the form of widely diffused miliary gummas. This condition may lead later on to a diffuse formation of connective tissue of what may be termed the pericellular type; not only at the periphery of the lobules but within the lobules themselves, separating off individual cells and cell columns, there may be developed a delicate but extensive connective tissue. Occasionally in acquired syphilis we meet, in the so-called late secondary stage, a similar enlargement of the organ with a like diffuse pericellular cirrhosis; also (though this must not be considered a true cirrhosis) in the neighborhood of large gummas we observe a similar pericellular fibrosis.

Fig. 331
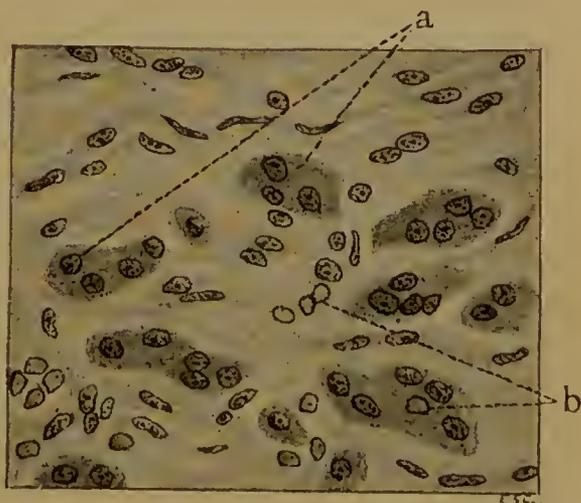
Section from a syphilitic liver showing diffuse pericellular cirrhosis: *a*, small detached clusters of liver cells; *b*, intralobular connective-tissue formation.

French authorities lay stress upon a somewhat similar diffuse fibrosis seen in some cases of tuberculosis, and ascribe this to the action of tubercular toxins; although we have sought for it, we have not seen this form. One of us (A.) has seen and described an extreme condition of pericellular cirrhosis in cattle suffering from what is known as **Pictou cattle disease**, now recognized as due to the effects of eating ragwort.

Inflammation of Glisson's Capsule.—This should strictly be considered as a localized form of peritonitis; it may be acute or chronic. We mention it here because one remarkable type of chronic progressive inflammation has often, from the accompanying extreme ascites and great shrinkage of the liver, been mistaken for a portal cirrhosis. This is **hyaloserositis**, or **"cake-icing liver,"** in which there is a dense, porcelain-white, fibrous deposit sometimes a centimeter or more in thickness, particularly over the upper and anterior surface of the liver, which induces by its contraction great compression and atrophy. Some text-books teach that this is accompanied by an invasive cirrhosis of the liver tissues, but the cases we have seen have not shown any such process.

FIG. 332

Section from a gummatous, syphilitic liver, showing at *a* necrotic (gummy) central area; *b*, zone of leukocytes undergoing necrosis; *c, c*, zone of abundant small round-celled infiltration; *d d*, outer zone of fibrosis, extending outward between the columns of compressed liver cells at *e; f* bile duct.

The Specific Inflammations.—Miliary **tuberculosis** of the liver is not uncommon in cases of general disseminated hematogenous tuberculosis. Often the tubercles are so fine that they are noticeable only upon microscopic examination, and then also it is characteristic that in general they are isolated and show little caseation and appear as though they develop with difficulty, suggesting that the tubercle bacilli do not readily multiply in this organ. Occasionally, however, as in the brain, we encounter solitary conglomerate masses of caseating tubercles, **tuberculomas**. A

third form, the so-called **bile-duct tuberculosis**, is described in which tuberculous nodules up to the size of 1 or 2 cm. in diameter, are distributed along the course of the larger bile ducts. These show a caseous centre, are apt to be bile-stained, and what is more, they tend to break into the bile ducts and so to undergo cavitation.

Syphilis.—It may sound paradoxical but at the same time it is true that of all the internal viscera the liver shows most frequently manifestation of the presence of syphilis, and nevertheless, considering the frequency of acquired syphilis, it is somewhat striking to observe how rarely in the ordinary run of post mortem cases we meet with syphilitic disturbances in this organ. Or otherwise, with modern treatment it is rare to find permanent syphilitic disorders of the viscera, but of the viscera the liver is most frequently involved. At the same time, the syphilitic lesions are very varied. Considering first *congenital* syphilis, common conditions are either widely disseminated miliary gummas or a later stage of syphilitic cirrhosis, but in addition there are some few cases on record of large solitary **syphilomas**, corresponding to the tuberculomas already mentioned, surrounded by hyperplastic liver parenchyma. Ordinary gummas of moderate size are comparatively rare in the congenital disease. In *acquired* syphilis, it is these ordinary gummas and the results of the same that are the commonest and most characteristic mani-

Treponemas in gumma of the liver of a new-born child; note the general disintegration of the liver substance which is unrecognizable. × 880. (Sauvage and Gery.)

festation. We may find either infrequent nodules moderately sharply defined with gummy centres, which may be 2 or 3 cm. in diameter, or more frequently there is present one or other later stage in the history of the same. The tendency is for these gummas under ordinary conditions to undergo absorption. With this, the necrosed centre undergoes shrinkage and simultaneously there develops a very pronounced surrounding fibrosis. This often takes the form of radial processes of fair size extending for some little distance between the lobules. The shrinkage that this inflammatory fibrous tissue may undergo is very striking, and the result is that the overlying liver tissue is pulled in and the surface of the liver shows well-marked distortion,

resembling, to employ a homely simile, a seat upholstered by the button method, there being deep impressions with stellate furrows radiating from the bottom of each. Where these cicatrices are abundant we obtain the greatly distorted, coarsely lobate liver, the **hepar lobatum.** This distortion appears to be permanent; we may, in old syphilitics, meet with these depressions which show at their base a small amount

Fig. 334
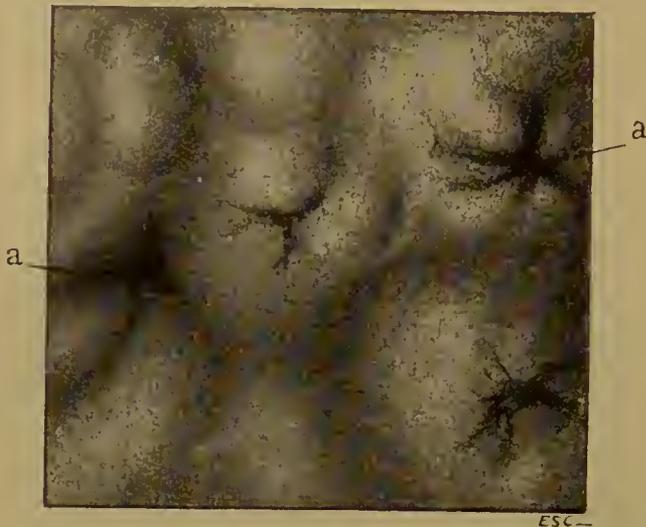
Surface of syphilitic liver to show the characteristic puckering (*a, a*) over old fibroid gummata.

of cicatricial tissue, running into the liver tissue, but exhibiting no sign of the typical gumma, the gummy matter having been wholly absorbed. As already noted, there may be, though rarely, a diffuse syphilitic cirrhosis, and somewhat more frequently than in the congenital form we may similarly encounter huge solitary syphilomatous masses, which may easily be mistaken for tumor growths.

Speaking of errors of diagnosis, it deserves mention that the syphilitic cicatrices if situated near the hilus of the liver may so compress or pull upon the larger portal veins as to cause obstruction and ascites and lead to a supposition that we deal with a case of portal cirrhosis.

Actinomycosis.—Actinomycosis is somewhat apt to involve the liver as a metastatic process, and there may be multiple small, granulomatous areas or, more characteristically, solitary large masses, many centimeters across, characterized by a somewhat spongy appearance.

Regressive Changes.—Atrophy.—Simple atrophy is seen in old age, as also in severely cachectic conditions. The organ is small, with sharp edges, and, particularly in the left lobe, along the edge, there may be complete disappearance of the liver cells, the connective tissue framework alone remaining as a whitish continuation of the liver tissue. Under the microscope, the lobules, columns, and cells are small, and throughout, the cells may show small accumulations of brownish pigment (**brown atrophy**).

Pressure Grooves.—These manifestations of partial atrophy are somewhat common, either shallow grooves corresponding to the ribs or as already noted, **Liebermeister's grooves** (p. 669), or as the **cardiac depression** (p. 670), or, lastly, as the groove that separates the so-called "lacing-lobe," brought about by excessive and long-continued tight lacing, by which the liver is forced down and the costal edge pressed into it. In one case known to us the terminal portion of the right lobe was found lying in the pelvis attached to the rest of the liver by a long fibrous band.

Degenerations and Infiltrations.—These are many and frequent. Most common is the **cloudy swelling** seen in acute infections and early toxic states. Frequent also are **fatty infiltration** and **fatty degeneration**, the former in cases of obesity and overfeeding, alcoholism, conditions of deficient oxidation, *e. g.*, some cases of tuberculosis and other cachexias, and lastly, in the late stages of pregnancy. While the peripheral cells are the first involved, it may be noted that in the pregnant woman the central cells of the lobule may contain the largest store of fat. We may recall that in this form, while the cell nucleus still stains well, the cell body is seen distended by one or more large fatty globules. **Fatty degeneration** proper is evidenced by the appearance of multiple minute granules or fine globules of lipoid or fatty matter throughout

FIG. 335
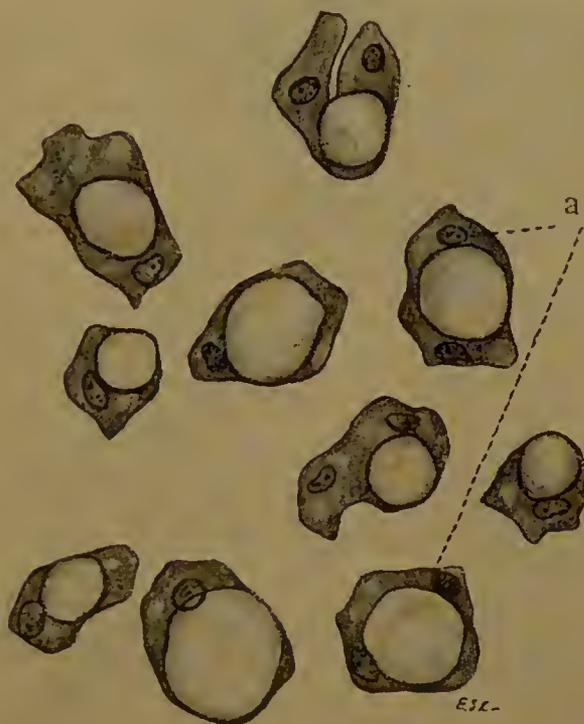
FIG. 336

Teased cells from a fattily infiltrated liver: *a*, nuclei being pushed to the periphery.
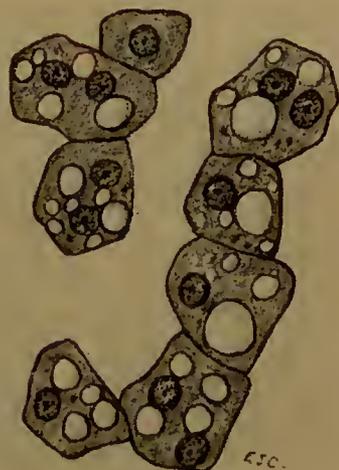
Teased cells from a liver showing the earlier stage of fatty infiltration, with multiple fat droplets of varying size distributed in the cytoplasm.

the cell body, accompanied in typical cases by evidence of nuclear chromatolysis and degeneration. One of us (McC.) with Professor Klotz has called attention to the frequency of this condition and has suggested that the irregular and angular form of the granules, when stained with Sudan III, indicates that we deal not with ordinary neutral fats but with some fatty compound or lipoid. This fatty degeneration may be either universal, peripheral, or central in position in the lobule, but there is no evidence to indicate the meaning of particular distribution; it is notable that in pernicious anemia the degeneration is generally of the central type. As a further distinction between the liver of fatty infiltration and that of fatty degeneration, it may be said that in the former, the organ is large, with round, obtuse edges, pale and solid,

with a greasy cut surface, while in the latter, the liver is flabby, shrunken, brittle, and of a more natural color. In phosphorus poisoning and in acute yellow atrophy we appear to have a combination of infiltration and degeneration.

FIG. 337
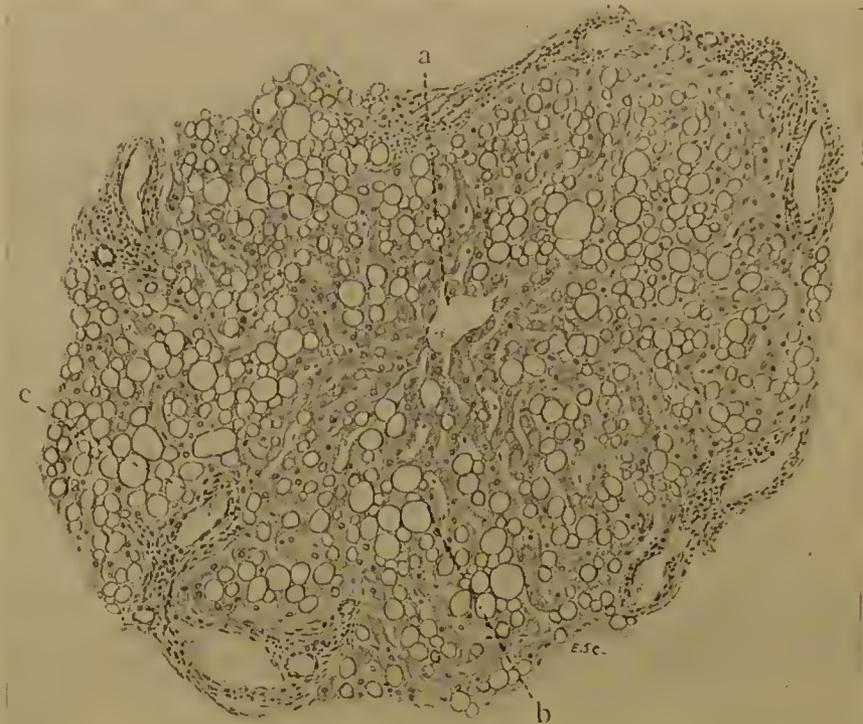
Section from the liver of an alcoholic, with fatty infiltration and slight grade of fibrosis in the portal sheaths: *a*, central vein; *b*, a fatty liver cell.

Glycogenous infiltration may be encountered in the peripheral cells of the lobule in certain cases of diabetes; in some of these cases recently the glycogen has been detected actually within the nuclei.

Amyloid of the liver is seen in general amyloidosis, associated with similar change in the spleen and kidney; when advanced, the liver is enlarged, firm, and the waxy areas are prominent on the smooth cut surface. Microscopically, it may be observed that the deposit occurs first in the intermediate zone, that is, the zone midway between centre and periphery of the lobule; later, the amyloid deposit may affect the whole lobe, causing great atrophy of the liver cells proper.

Pigmental Infiltration.—The pigment deposited in the liver may be of different kinds, viz., bile pigment (bilirubin), iron-free derivatives of blood pigment, and hemosiderin. In **icterus** or jaundice the heaping up of the pigment is seen primarily within the liver cells and here at times it can be recognized that it occupies a set of fine intracellular channels. In more advanced cases the inspissated bile is found also in the bile capillaries between the liver cells and deposited in the lymph spaces of the portal sheaths. According to degree of pigmentation, the liver may exhibit a bright yellow, a pronounced brown, or even a dark olive-green color upon section. We have considered the causation and forms of icterus on p. 290.

Iron-containing pigment is recognized in the form of fine (**hemosiderin**) granules situated along that border of the cell which impinges upon the bile capillary; in advanced cases it may be seen even in the periportal connective tissue; it takes on a Prussian-blue stain with solutions of potassium ferrocyanide after treatment with acid, and is very pronounced in cases of pernicious anemia, hemochromatosis, and those intoxications in which there is excessive destruction of the red blood corpuscles. The liver in these cases has a distinct rusty-brown color on section, unless the fat is so extreme as to give it a paler yellow. Accompanying this iron-containing pigment there are generally to be seen yellowish pigment granules which do not give the Prussian blue reaction; these are spoken of as **hemofuscin**. Similar granules, often agglomerated, are to be recognized in the atrophying cells in the condition of **brown atrophy.**

A characteristic form of pigmentation may be encountered in recurrent **malaria** when the liver assumes a bluish-grey or even a dark chocolate color. The pigment in these cases is found in abundance in the endothelial cells lining the portal sinusoids and capillaries as also in **Kupffer's star-cells**, occasional cells which, on the one hand, impinge upon the blood stream and so have an endothelial character, and on the other penetrate between the liver cells. This pigment is obviously derived from the central pigment deposits in the bodies of the hemamœbæ, left free in the blood after sporulation, and obviously also is a metabolic product of the hemoglobin of the erythrocytes absorbed by the growing parasites.

Calcification.—There are on record a few cases of extensive calcification of the liver associated with previous extensive necrosis of the lobules.

Necrosis.—The commonest form of necrosis in the liver is met in the form of multiple minute and discrete areas of cell death, in many *acute infections*. Experimentally these can be produced by several toxins. We have discussed the theories regarding their causation on p. 296. In *chloroform poisoning* more extensive necrosis may be seen affecting the central zone of the lobules and in *pernicious anemia* occasionally a similar central necrosis may be found. More extensive areas of necrosis may occur in *eclampsia*, the etiology of which is still unknown. The necrosis may be extreme, involving a large part of the entire tissue of the liver. Similar very extensive necrosis characterizes the condition of **acute yellow atrophy** and an almost identical picture is seen in acute **phosphorus poisoning**. In any of these states, where the toxin has evidently been very strong, followed quickly by death, the cells are found in a condition comparable with coagulation necrosis; their general form and relationships are unaltered, although they fail to take nuclear stains; in less sudden cases, where presumably the toxin is less acute, there is seen a peculiar disarrangement or "jumbling" of the cells so that the orderly arrangement of the cells in the lobule is wholly lost. The cells no longer give the Sudan III reaction for fat. (McCrae and Klotz.)

It used to be the custom to consider acute yellow atrophy as a condition *sui generis*. Now we are coming to recognize that several

FIG. 338
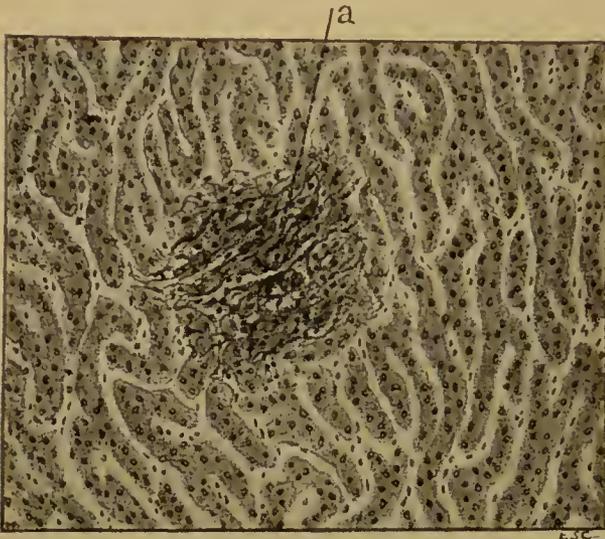
FIG. 339

Focal necrosis. Section from a typhoid liver exhibiting at *a* the early stage of uncomplicated necrosis of a small area.
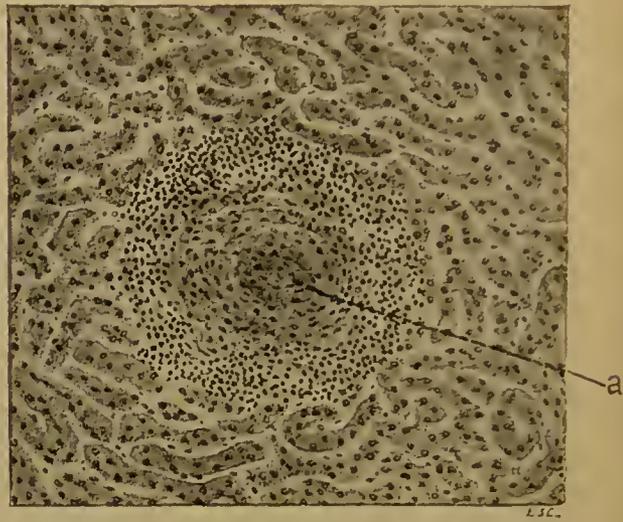
Section from the same liver exhibiting a later stage of focal necrosis with small-celled infiltration into the necrotic area: *a*, necrotic centre. In a later stage the small cells completely remove and replace the necrosed liver cells.

FIG 340

Section from the liver showing well-marked central necrosis of the lobule: *a*, centre of lobule with few and shrunken remaining liver cells; *b*, portal vein; *c, c, c, c*, portal sheath at periphery of lobule.

different intoxications, such as the eclamptic, phosphorus poisoning, and the exhibition of chloroform may all produce a very similar picture,

so that the term acute yellow atrophy must be applied only to those conditions of extensive necrosis in which the causative agent remains undetermined. Such cases seem more frequent in women than in men; in the earlier stage the shrunken liver has externally and on section a

FIG. 341
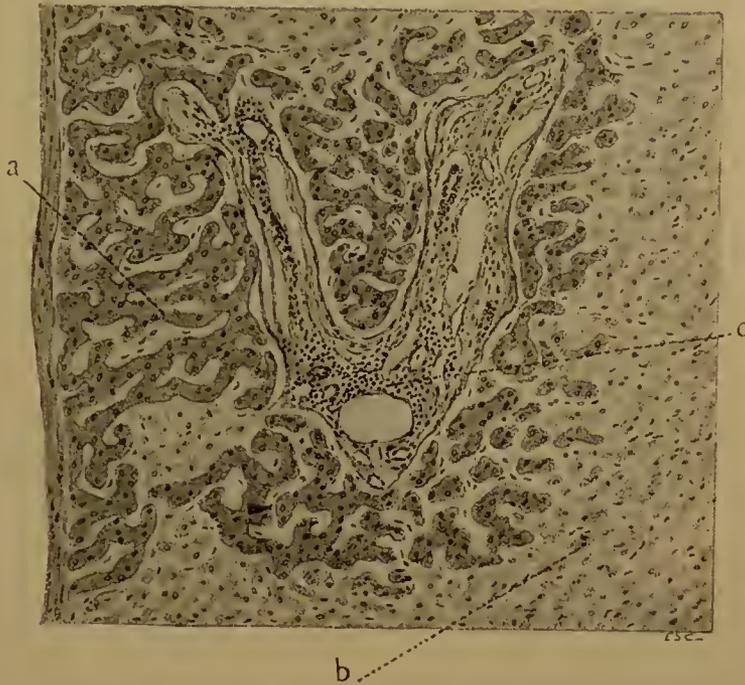
Section of liver from a case of eclampsia showing widespread necrosis: *a*, liver cells relatively unaffected, still retaining normal arrangement and staining powers; *b*, necrosed liver cells; *c*, a portal sheath, with some small-celled infiltration.

FIG. 342
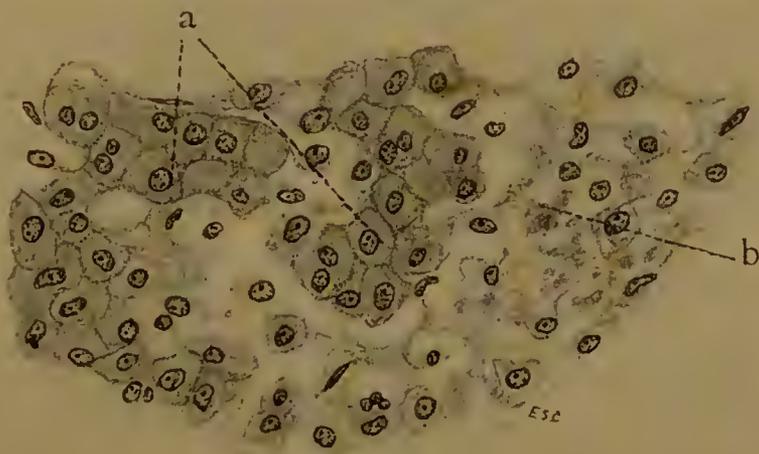
Section from the same liver under higher magnification, showing the sudden transition from the relatively healthy (*a*) to the necrosed tissue (*b*). The "jumbling" of the affected cells is well shown.

bright yellow appearance (yellow atrophy). With complete necrosis and disintegration of the cells there follows an adaptive dilatation of the capillaries with occasional hemorrhages, so that now intensely congested areas alternate with or are interspersed among those still

retaining the yellow color (**acute red atrophy**). In cases of red atrophy not rapidly fatal there is further an extensive small-celled infiltration with indications of active regeneration in the form of budding and worm-like processes from the bile ducts. It seems probable that with recovery there may develop a cirrhotic condition.

Progressive Changes.—**Hypertrophy and regeneration** of individual lobules may be seen as above noted in non-fatal cases of necrosis, and also in cases of portal cirrhosis, where nodular areas of such regenerative hyperplasia are seen; as already stated these may pass on to irregular multicentric adenomatous or even carcinomatous overgrowth. Loss of liver tissue is followed by no new formation of lobules but those in the neighborhood of the loss undergo pronounced enlargement, the cell columns actually proliferating. It is now fully established that regeneration may occur by two processes, viz., by budding from preexisting bile ducts or by proliferation of preëxisting liver cells.

Tumors.—**Cavernoma.**—A common abnormal condition found in the liver is the presence of one or more, sharply defined, generally small areas of deep red color (see Figs. 200 and 201). On microscopic examination these are seen to be composed of greatly dilated, communicating capillary channels filled with blood or containing thrombus, with no intervening liver cells. We have discussed these on p. 396 and pointed out that strictly speaking, they are not tumors proper.

True **fibromas** and other benign connective-tissue tumors are rare. So also primary **sarcoma** and **hemangioendothelioma** are infrequent. On the other hand, secondary **sarcomas** are not uncommon, and the liver is notably a favorite seat for multiple metastatic **melanotic sarcomas**. A few cases are on record of included adrenal tissue, and of tumors, **hypernephromas** or **mesotheliomas**, originating from the same. Two forms of **adenoma** are to be recognized, viz., the tubular adenoma, evidently originating from and to some extent reproducing the cubical or columnar epithelium of the bile ducts, and the true liver-cell adenoma, in which the cells are arranged without lumina and reproduce irregularly the structure of hepatic parenchyma. The multiple nodules of hyperplasia already described partake of this type.

Solitary primary **carcinoma** of the liver is rare; a large solitary metastasis from some minute and obscure primary focus must not be mistaken for such a primary growth. In short, very careful search must be made before declaring any case to be one of primary carcinoma of the liver. A considerable number of cases of diffuse carcinomatosis secondary to cirrhosis are recorded. A small-celled form of carcinoma of scirrhous type is by some held to originate from the bile ducts. In considering any hepatic carcinoma, the possibility of its origin from the gall bladder must always be kept in mind, considering the great frequency of cancer of this organ.

While thus primary carcinoma of the liver is distinctly uncommon, there is no organ in the body which is more frequently the seat of secondary cancerous growths; more particularly in carcinomas of the

stomach, pancreas, œsophagus, intestine, and ovary, is the liver apt to be affected, and the secondary growths may be extraordinarily abundant and some of them of very great size. As a consequence the liver may be relatively enormous, the nodules often being palpable through the skin. On examination of such a liver the nodules stand out as well-defined masses, whitish against the congested liver tissue; the surface nodules frequently present umbilication (a crater-like depression) owing to autolysis and absorption of the central areas.

Cysts.—Hepatic cysts are of two main orders, **retention** cysts, and **parasitic** cysts, due to the growth of echinococcus within the organ.

Bile cysts may be solitary, due to the obliteration of an individual bile duct, either congenital or acquired, or may be small and multiple, scarcely visible to the naked eye; this last condition is seen in what has been termed cystic degeneration of the liver, a congenital state found sometimes associated with similar multiple cystic development in the kidneys and, it may be, also in the pancreas. The contents of bile cysts are generally watery in appearance. Rare cases are described in which cysts due to congenital abnormality of the bile ducts possess a ciliated epithelium.

Parasitic cysts are due to the development in the liver of the echinococcus in its encysted stage (**hydatid**). This cystic phase in the life history of Tænia echinococcus may take on two main forms, in one of which the formation of daughter cysts takes place wholly on the inner aspect of the capsule, and in the other, rarer form, on the outside, so that numerous outlying smaller cysts develop (**multilocular**), so abundant and widespread as to give the appearance of a colloid cancer. The capsule of the hydatid is double, consisting of an outer fibrous layer provided by the irritated tissue of the liver, and an inner hyaline layer, the cyst wall proper of the parasite. The presence of hooklets in the fluid, recognizable by the microscope, is the characteristic diagnostic feature. Occasionally the parasites die, and the cyst contents undergo absorption, being ultimately represented by a fibrous cicatrix with an irregular shrunken cavity in which hooklets may still be found. Some three or four cases of **coccidiosis** of the liver are on record. Other parasites of the liver, not causing cyst formation, but lying in the bile ducts, to which they have gained entrance from the duodenum, are **distomum** (several species) and rarely **ascaris lumbricoides**.

GALL BLADDER AND DUCTS

Abnormalities.—Complete **absence** of the gall bladder has been recorded and occasionally it may hang completely free from the liver. Its relation to the liver edge is very variable. An important abnormality is **congenital atresia** or **complete obliteration** of the common bile duct, leading, with progressive jaundice, to inevitable death. Remembering that the liver is a tubular outgrowth from the duodenal region,

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it is obvious that such obliteration must occur after the definite differentiation of liver and ducts.

Circulatory Disturbances.—Œdema is a not infrequent condition associated with general anasarca. Submucous **hemorrhages** are occasionally seen.

Inflammation.—There is still debate as to how bacteria most commonly enter the gall bladder, whether by excretion through the liver from the blood or by ascent of the duct from the duodenum. This much, however, is clear, that at operation and at post mortem a large proportion of samples of gall bladder bile afford cultures of one or more forms of bacteria; the presence of these bacteria favors the development of cholecystitis. This inflammation may be of various orders. The commonest is simple **catarrhal cholecystitis**, an inflammation characterized by congestion, active proliferation and freeing of the columnar cells of the mucosa into the bile, together with markedly increased excretion or discharge of mucin. The mucosa is found swollen, turbid, infiltrated with round cells, and covered by a layer of mucin, and inasmuch as the common and cystic ducts may be involved (**acute cholangitis**), the swelling is apt to lead to obstruction and as a sequence to jaundice (**acute catarrhal jaundice**). This condition may be recurrent or continued over long periods, and then associated with a polypoid overgrowth of the mucosa of the gall bladder or sometimes with secondary atrophy and thinning. Particularly in these long-continued cases, as already noted on p. 288, the altered composition of the bile, and the presence of cell debris and of mucus, and the direct action of the bacteria from the bile, together with its stagnation, act in concert as factors in the production of gallstones. Once formed these gallstones in themselves act as a continued irritant and in this association it is interesting to note that over 90 per cent. of the cases of cancer of the gall bladder afford a history of the presence of gallstones.

Suppurative cholecystitis is most frequently found associated with these same gallstones, but may present itself in cases of severe infection, *e. g.*, some cases of typhoid and pyemia. Very frequently such suppuration is seen to be secondary to complete or partial obstruction of the cystic duct from preceding non-purulent inflammation. As in the appendix, so here, stagnation appears to favor the proliferation and increased virulence of bacteria, so that what was previously a simple becomes now a suppurative process. Associated with this purulent condition there may be necrosis of the mucosa with ulceration, and at times gangrene of the deep layers of the wall and perforation; as a result there may be either a localized **purulent pericholecystitis** (localized peritonitis) or general peritonitis. The bile, when it escapes into the peritoneal cavity, as pointed out by Bunting, has in itself direct irritative and necrotic effects. This necrosing, ulcerative form of cholecystitis is often accompanied by a superficial membrane formation upon the inner surface of the gall bladder; more rarely this is seen in the large bile ducts. The suppurative form may occur not only in the gall

bladder but also around impacted gallstones in the ducts. From this perforation either of the gall bladder or of the larger ducts, there may result, not necessarily escape of the contents into the abdominal cavity, but where time has been afforded for adhesion with neighboring organs, the contents may make their way into the interior of viscera. Notably there may be fistulæ between the gall bladder and bile ducts, on the one hand, and the stomach, duodenum, ileum, colon, or the skin on the other. There is scarcely an organ of the trunk that has not been the seat of such fistula.

Two widely contrasted states of the gall bladder resulting from inflammation may at times be encountered. With obstruction and suppuration the organ may be hugely distended, and on section found to be converted into a bag of pus; on the other hand, in cases showing evidence of long-continued inflammation without destruction, the laying down of increased fibrous tissue in the submucosa is followed by pronounced contraction, so that the organ may be represented by a mass, as long as and not thicker than a finger, practically shrunken up and devoid of contents. Not infrequently this latter condition is associated with extensive organized adhesions to surrounding structures, evidence of a previous acute inflammation.

As originating from previous inflammatory disturbances, though in itself not a sign of active inflammation, there may be noted the striking condition of **hydrops cystidis felleæ**: the gall bladder is found pale or almost translucent, greatly distended, and on section discharges a fluid wholly devoid of bile but shimmering, if not milky, with abundant cholesterin crystals. The process in the development of this condition is usually catarrhal inflammation with obliteration or blocking of the cystic duct, either by overgrowth of the mucosa or by means of a stone. The contained bile diffuses out and at the same time fluid and mucus are discharged from the mucosa, leading to progressive distension. The abundant cholesterin suggests that there is a continued state of mild inflammation of the mucosa, with dissociation of the epithelial cells or actually increased excretion of cholesterin or some precursor thereof, such as cholesterin oleate.

The infective **granulomas** rarely affect the gall bladder and larger biliary passages.

Progressive Changes.—Tumors.—The main tumor to be considered in connection with the gall bladder and bile ducts is **carcinoma**. Benign tumors are so rare that they may be passed over; the same is true of the primary **sarcomas.**

Carcinoma most often originates in connection with the gall bladder, but may also occur along the course of the larger ducts, either in the cystic duct, or, at its junction, within the common duct or again at the ampulla of Vater. Carcinoma of the gall bladder most frequently shows itself either in the fundus or at the neck; at the fundus, either through the gravitational presence of gallstones, or at the neck in association with the arrest of the same in their passage to the duct. We

would here emphasize that this is one of the frequent sites of carcinoma, roughly 5 per cent. of cases of carcinoma arising here. The typical form is a soft, columnar-celled adenocarcinoma tending on the one hand to form a mass projecting into the gall bladder, and on the other to infiltrate extensively the wall and the liver tissue; but variations are found. At times, there is abundant stroma formation with alveoli filled with round cells and the general characters of a scirrhous growth, and several examples are now on record in which through metaplasia, presumably due to preceding inflammation, the tumor approximates to the squamous-celled epitheliomatous type or shows a combination of epitheliomatous and adenocarcinomatous structure (see Fig. 192, p. 389). There may also be, though rarely, cases of colloid cancer. Here, as in cholelithiasis, the condition is more common in the female than in the male. In addition to the direct infiltration, there are apt to be large nodular metastases in the lymph nodes at the hilus and in the mesentery, and in the peritoneum, as well as isolated nodular metastases in the more distant parts of the liver. Carcinomas of the larger bile ducts are of the same type as those of the gall bladder, though in our experience they lead to death more rapidly than do the latter, and as a consequence are found of smaller size. From their region of origin, they necessarily lead to obliteration of the common bile duct, and to fatal jaundice or through their ulcerative character to infection. Carcinomas of the ampulla of Vater, it must be remembered, may originate either from the mucous membrane of the terminal portion of the bile duct or from the duodenal mucous membrane covering the ampulla.

Secondary cancers, involving either gall bladder or bile ducts, are uncommon.

THE PANCREAS

Like the liver, although in a different way, the pancreas subserves multiple functions; as regards its excretion, it affords a trypsinogen which, combined with the enterokinase supplied by the mucosa of the small intestine, affords the most powerful proteolytic ferment of the organism; wherefore it follows that arrest of this excretion, either by obliteration of the duct or atrophy or arrested activity of the gland cells, is followed by incomplete dissociation of the proteids of the food, and consequent lack of assimilation of the same, so that, as a matter of fact, a condition of true starvation is brought about and a progressive emaciation developing more rapidly than from any other cause.

It also excretes a lipolytic ferment, steapsin, essential to the dissociation and subsequent absorption of the fats; interference with or absence of this excretion is also a potent factor in the emaciation above mentioned. In such conditions we find that the stools are clay-color from excess of unaltered fats. Other ferments are produced, notably an amylolytic or starch-splitting ferment.

Equally important seems to be the internal secretion afforded by

this organ; we have discussed this on p. 99, but we would here recall
that there is in the body a "sugar combine" or "trust," of which the
pancreas, the liver, and the muscles are the members, which controls
the amount of sugar formed and its consumption in the organism, so
that atrophic or degenerative disease of the pancreas is associated with
the development of **glycosuria**. Not all cases of diabetes present
pancreatic changes, for it is evident that certain lesions of the other
members of the "combine" may lead to a similar loss of control of output.

Abnormalities.—These are not very common, but we occasionally
encounter **hypoplasia** or even **absence** or **duplication**, or again, more
commonly, the presence of small **accessory groups of pancreatic acini**
either in the submucosa of the stomach, the duodenum, or even the small
intestine. The most important irregularity in the development of the
organ is in connection with the ducts. The original pancreas was
possessed of two ducts, one, the duct of Santorini, from the head of the
organ, the other, Wirsung's duct, constituting the main duct of the
body of the gland. In the course of development these become con-
nected within the body of the pancreas and the duct of Santorini
undergoes atrophy, so that most cases eventually come to present
only a single duct opening into the ampulla of Vater. In 10 per cent.
of all organs examined, there is persistence of the former duct with a
papilla, generally minute, opening into the duodenum at a somewhat
higher level than the ampulla. It is obvious that the presence or absence
of this duct of Santorini with its communication with the main duct
will materially modify the results of obliteration or obstruction of
the duodenal end of the main duct. Variations also occur in the
relations of the duct of Wirsung to the common bile duct. The two
ducts may open into the duodenum side by side, one at the very termina-
tion of the ampulla, the other slightly separated from it; but usually
the pancreatic duct gains entrance to the bile duct at the base of the
ampulla so that the ampulla constitutes what may be termed a pancreat-
ico-hepatic duct, a centimeter or more in length. These relationships
also are of material importance in determining the results of blockage
of the ampulla by a small gallstone, etc. As a result of such blockage,
according to the relationships, the dammed back bile may or may not
enter the pancreatic duct.

Circulatory Disturbances.—The pancreas is abundantly vascular but
on account of its natural color, it does not show to the naked eye any
marked changes in anemia; in cases of **passive congestion**, it becomes
large, injected, and of a bluish-gray color, whereas in active **hyperemia**,
such as occurs during digestion, it is found of a pinkish color.

The most important circulatory disturbance is the supervention of
hemorrhage in the gland and the development of the falsely so-called
acute hemorrhagic pancreatitis. The series of events leading to this
condition is now generally acknowledged to be (1) the development
of local areas of ischemia of the gland substance by arterial arrest or
disease; (2) the cells in these areas undergo necrosis with the libera-

tion into the tissues of the cellular ferments; (3) localized self-digestion ensues with erosion of the capillaries and other vessels, associated with which there is necrosis of the fat cells in the neighborhood and dissociation of the contained fat through the agency of the liberated steapsin (**fat necrosis**). The condition is by no means necessarily of infective origin; around such areas there may be, it is true, evidence of acute inflammation, but this is secondary. The effects of these liberated ferments are not confined to the pancreas but may involve surrounding tissues; the condition may be rapidly fatal within a few hours or, on the other hand, there are evidences that, if not extensive, recovery may ensue.

Inflammation. — There is a possibility that a condition similar to the above may follow a localized inflammation in the pancreas and that there is thus a true acute necrotic and hemorrhagic pancreatitis, but if so, bacteriological studies show that this is the exception and not the rule. **Purulent pancreatitis** is occasionally encountered, either with multiple small pyemic abscesses in cases of bacteriemia, or by extension of disease elsewhere, oftenest by perforation of a gastric or duodenal ulcer, or lastly, by an ascending inflammation of the pancreatic ducts.

Chronic Pancreatitis. — It has been experimentally shown by Opie and others that by obstruction or, again, by retrograde flow of bile into the pancreatic duct, there may develop a condition of fibrosis around the duct and its branches, due to resorption of the secretion as well as to the irritation of the foreign fluid. Whether this be the essential cause or no, it is to be remembered that in cases of cholelithiasis we frequently encounter a marked induration especially of the head of the pancreas, this becoming so firm that the surgeon is apt to mistake it for new-growth. The organ also is apt to show extensive fibrosis in advancing age, associated with the chronic periarteritis of arteriosclerosis. We thus recognize more than one form of fibrotic change in the organ, viz., a **centrilobular**, around the branches of the duct, a **perilobular**, separating the individual collections of somewhat atrophic acini from each other, and an irregular, or **sporadic** form, secondary to previous inflammation or necrosis of localized areas. It is to be noted that a chronic diffuse pancreatitis or cirrhosis is not infrequent as an accompaniment of cirrhosis of the liver.

Infective Granulomas. — **Tuberculosis** is very rare. As a result of congenital syphilis, there may be encountered an extreme grade of diffuse interstitial pancreatitis with enlargement of the organ, and induration and pronounced atrophy of a great part of the pancreatic tissue proper, save the islands of Langerhans. We are inclined to regard the islands of Langerhans as the mother tissue from which new acini may be developed throughout life, and in this and other forms of fibrosis the persistence of the islands indicates that this vegetative or mother tissue is the last to be destroyed. Others, however, it must be noted, regard these as independent entities.

Regressive Changes.—Care must be taken to distinguish between ante mortem and post mortem changes in this organ. If death occurs when the cells are in an active state, there is a marked tendency for the intracellular enzymes to diffuse out, and bring about a condition of post mortem **self-digestion.** In the early stages of this process the organ may be firm, opaque, and homogeneous, and on section the nuclei either stain feebly or fail to stain. This condition resembles somewhat coagulation necrosis; at a later stage softening takes place with disorganization. In discussing the so-called hemorrhagic pancreatitis we have already described the main features of the commoner forms of

Fig. 343

Section from a fibrosed pancreas, showing a combination of the centrilobular and perilobular types; there has been obstruction and dilatation of the main ducts (*a*) and their branches (*b*). The lobules are separated by broad perilobular bands of fibrous tissue, and the individual acini (*c*) in the lobules are similarly separated by a centrilobular fibrosis.

antemortem or intravital necrosis and self-digestion. In general, this affects part and not the whole of the organ, and areas are observed in which the pancreatic acini still preserve their normal staining power. Occasionally, however, at operation or post mortem it is found that practically the whole of the organ has undergone ante mortem self-digestion. The appearance in such cases is very remarkable; in the region where the pancreas ought to be there is found a mass of completely degenerated softened "muck," blood-stained, shreddy, greasy, with intense surrounding inflammation and tendency to generalized peritonitis. Throughout the peritoneal cavity in such cases there may

be found foci of fat necrosis. This extensive necrosis may follow not merely the causes above mentioned, namely, stasis, vascular obliteration and infection, but may, as in the case of the late President McKinley, follow trauma, or, again, operative section with liberation of the pancreatic juice.

Regarding the relationship of the pancreas to diabetes mellitus, while admitting that the matter is still unsettled, we are inclined, as a matter of clearness, to lay down the following: (1) in a considerable proportion of cases no change can be observed in this organ; (2) in the rapidly progressive cases of early life there is a hydropic degeneration of the islands of Langerhans followed by atrophy, with little accompanying general fibrosis of the organ, although there may be considerable atrophy of the general parenchyma (Weichselbaum); (3) the slowly evolving diabetes of advanced life may be characterized by marked fibrosis and atrophy of the organ in general, together with changes in the islands. These changes are most often of the nature of a hyaline degeneration or infiltration. With regard to the relationship of these islands to the pancreatic acini there are data favoring the view that they play a part in the sugar regulation of the economy.

A frequent form of regressive change in the pancreas is **fatty infiltration**. In advanced cases the greater part of the gland substance may have atrophied without the organ being reduced in size, a fact which is due to its replacement by fat cells; often localized areas of such fatty infiltration occur. **Fatty degeneration** of the gland cells has been noted in phosphorus poisoning. **Fat necrosis** has already been discussed. **Amyloid** change is to be seen in general amyloidosis.

Single or multiple **calculi** may be encountered in the larger ducts; they are formed of calcium salts with a mucinous matrix and are due to an accumulation of cell debris following catarrhal inflammation.

Progressive Changes.—Tumors.—We rarely encounter benign growths in the pancreas. In our laboratory Nicholls has recorded localized **adenomas** arising from the islands of Langerhans, and since then, a few other similar cases have been placed on record. Others have described **cystadenomas** representing more fully differentiated pancreatic tissue. Connective tissue tumors are rare. The most important tumor is the primary **carcinoma**. Through the infiltrative qualities of both tumors, it is often difficult to say whether we deal with a primary pancreatic or a primary gastric tumor, especially where these are of a scirrhous or of a pronounced anaplastic type. Most frequently the growth originates in the head of the pancreas, and most frequently, also, is of a relatively scirrhous type, but soft, adenocarcinomatous growths are to be encountered, as are primary tumors originating in the tail or body of the organ. Growing in the head, these tumors are peculiarly liable to cause obstruction of the common bile duct, setting up a condition of grave icteric toxemia, accompanied by rapid emaciation when there is arrest of secretion, and extensive destruction of pancreatic tissue. The pancreas itself is apt to be extensively involved by the

infiltration of the growth; this infiltration is apt to extend to surrounding tissues, stomach, adrenals, etc., while abundant metastases occur in the lymph nodes and liver. Primary **sarcoma** is rare. Secondary melanotic sarcoma is liable to affect the organ.

Fig. 344
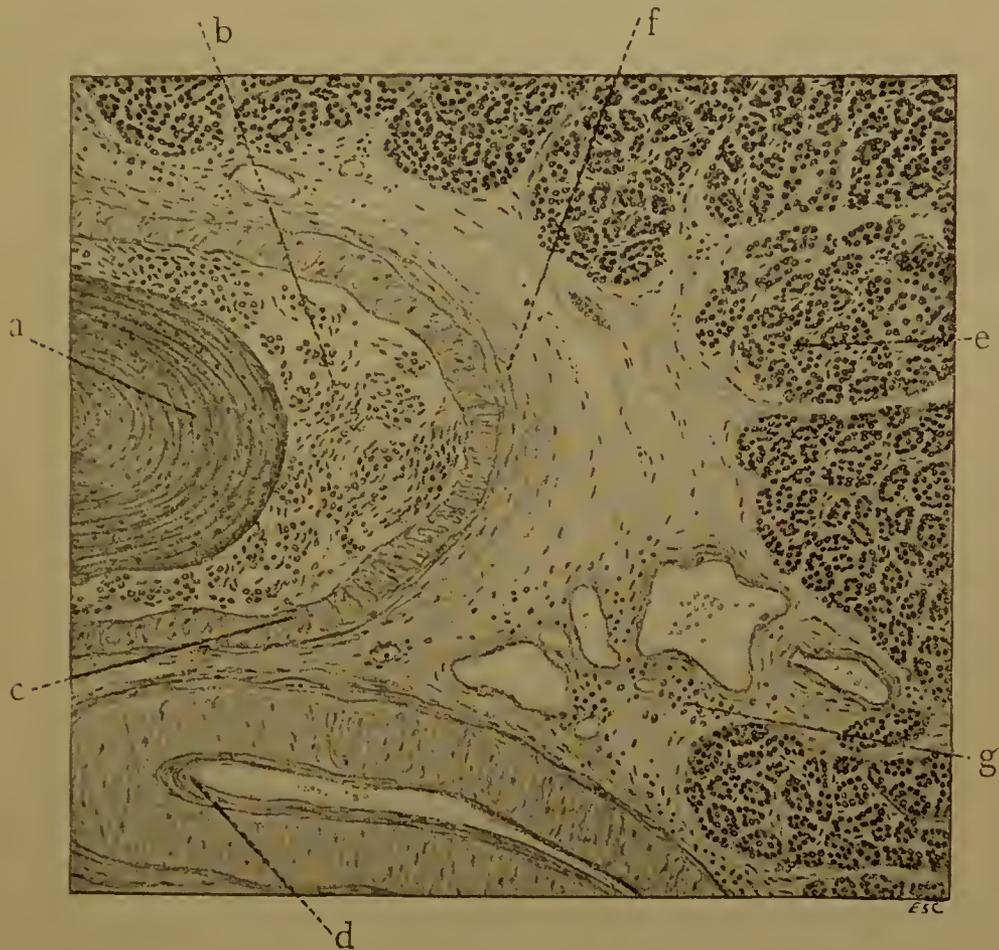
Pancreas: carcinoma extending along branch of portal vein: *a*, thrombus in vein; *b*, masses of cancer cells; *c*, wall of portal vein showing a certain grade of phlebosclerosis; *d*, artery; *e*, pancreatic acini; *f*, perivascular fibrosis; *g*, small-celled infiltration. (Dr. Rhea.)

Multiple **congenital cysts** occur along with similar cysts of the liver and kidney. **Retention cysts** of later life (**ranula pancreatica**) may be either solitary or multiple, may attain large size and are due to obstruction either from a concrement lying in the main duct or one of the branches or secondary to inflammation and obstruction of the ducts. These cysts are most often in the tail or body. **Echinococcus** cysts are recorded.

CHAPTER XI

THE URINARY SYSTEM

THE URINARY FUNCTION

General Considerations.—Embryology.—The permanent kidney appears about the fifth week of fœtal life, and is made up of cells from the Wolffian duct, on the one hand, and the mesoblastic tissue, called the blastema, on the other. The former gives origin to the ureter, pelvis, calices, and collecting tubules, the latter to the glomerular epithelium and the rest of the tubule. This complex origin and close relationship to the primitive myotomes suggest a partial explanation of the frequency with which mixed tumors (**teratoblastomas**) appear, and appear, too, in early life. The fact that the Wolffian body and the genital gland arise from the same primitive genital ridge, explains why developmental anomalies of the kidney and of the reproductive organs are so apt to occur together.

Anatomy.—The renal arteries are short and readily allow a transference of the aortic pressure to the kidneys; the kidneys are relatively abundantly supplied with blood, and theoretically all the blood in the body may pass through them in a short space of time, the result being that in any toxemic state of the blood, the kidneys are certain to bear the brunt of it in full measure. When they are damaged, the other secretory systems, the skin, the intestines, and the lungs must assume the responsibility for the work which the kidneys can no longer accomplish.

The kidneys possess abundant vasomotor nerves, and are therefore susceptible to central and peripheral impressions; the effect of mental states upon the amount of urine is well known, as is also the reflex effect often seen to be communicated from the bladder, genitalia, and rectum.

In the capsule of the kidney is a plexus of unstriped muscle fibres, recalling those seen in the spleen; the purpose of these is doubtless by contraction and relaxation to promote the circulation in the kidney and thereby modify excretion. Their anatomical position in the body, behind the peritoneum, protected as they are by abundant fat, ensures to the kidneys some immunity from trauma, while, on the other hand, communicating indirectly with the outside of the body, they are liable to certain extraneous infections.

The Physiology of the Urinary Function.—It is so usual for a gland to have an internal as well as an external secretion that we are tempted to conclude by analogy that the kidney, whose main work is obviously the production of an external secretion, may have also an internal one. At the present time, there is a little evidence in favor of this idea.

The analogue of the kidney exists in the secretory organ of the invertebrate, where we may find a ciliated opening leading from the cœlomic cavity into a tubule which passes to the outside. Since in the vertebrate the cœlomic cavity loses its importance as a medium of circulation, it is rational that the blood-vascular system should connect directly with the tubule, which it does by virtue of the glomerulus. The tubule, too, throughout its length, is in intimate association with the lymph, from which, again, the direction of flow is to the tubule and thence to the outside; yet not entirely so. We must recognize that a certain absorption occurs through the tubular epithelium back to the lymph, but there is little reason to suppose that this is a very important factor; for we find that the larger surface of the tubule is exposed to the lymph, the smaller to the urine.

Controversy has long waged over the question as to whether the action of the glomerulus and the tubule, in excreting the urinary water, is a mechanical or a secretory process; it may partake of both, but evidence seems largely in favor of the latter, especially when it is taken into consideration that definitely known metabolic processes, such as the building up of hippuric acid and other substances, take place in the renal epithelium. Brodie considers that the glomerulus, suddenly expanding under the influence of the arterial blood with the force of the heart beat, acts as a propulsor, that is, it forces the urine in Bowman's capsule into the tubule. While this is purely a mechanical proceeding, the endothelium of the bloodvessels and of the capsule is selecting what passes through.

The Vascular Supply of the Kidney.—The arterial supply of the cortex passes directly and almost entirely to the glomeruli. The blood enters the glomerulus in the afferent vessel, leaves it in the efferent vessel, and thence is distributed into a network of capillaries around the convoluted tubules. The blood supply of the collecting tubules in the medulla is from capillaries of the arteriæ rectæ. The blood supply of the cortical tubules, having been through one set of capillaries (the glomeruli) already is at a relatively low pressure, a state of affairs which suggests that this may allow a resorption from the urine, which is not

allowed in the collecting tubules where the blood pressure is higher. And in all probability this is what actually occurs.

Blood pressure determines to some extent the discharge of urine; if the general pressure be reduced to 40 mm. of mercury, the flow of urine ceases; but under relatively normal conditions, the *rate of blood flow* is of more importance than the pressure in the glomeruli. We conclude that certain simple salts (and though simple, selected) and substances such as grape-sugar, accompany the water through the glomeruli, and that while some resorption occurs in the convoluted tubules, a more important matter is the further selective excretion into the urine of urea, uric acid, and other "extractives," as well as toxins; and superadded, there is on the part of the cells a certain amount of metabolism, both anabolic and katabolic, of which the result is also discharged into the urine on its way through the convoluted tubule.

The Nerve Supply.—This is of considerable complexity; the nerves to the kidney form a plexus around the renal artery, and are for the most part vasomotor in function, both vasodilators and vasoconstrictors being demonstrable. Some nerve terminations must, on the other hand, be "secretory," for nerve terminals have been demonstrated in Bowman's capsule, and others entering the membrana propria of the convoluted tubules. Experiments upon the renal nerves have amply proved that these have a marked effect upon the amount of urine. The interlobular arteries are plentifully muscular and their state determines, to a great extent, the amount of blood in the glomeruli, in which, by the way, no nerves are demonstrable. The interlobular arteries, doubtless, may be overridden by the general blood pressure, and the degree of contraction or expansion of the capillaries may be affected by the substances that pass through their walls from the blood. To sum up, the amount of urinary water seems variable under the influences of (1) the central nervous system; (2) the intrinsic renal nerves; (3) the effect of substances in the blood on arterioles and capillary endothelium.

This may be expressed otherwise: the quantity of urine depends on the quantity of blood flowing through the glomeruli, and this blood flow depends on the difference in pressure between the renal artery and the renal vein; if the arterial pressure be increased without increase in the venous pressure, more urine is secreted; if the venous pressure be increased without increase in the arterial, less. At the same time the size of the arterial channels in the kidney must be taken into account; the urine is increased not only when the general arterial pressure is raised, but even if, without increase of general blood pressure, the interlobular and afferent arteries are dilated; on the contrary if the interlobular and afferent arteries are contracted without alteration of the general pressure, the amount of urine is diminished.

The ultimate object of all this mechanism is twofold; to regulate (in conjunction with the skin) the total amount of body fluid, and to separate from it substances that are unnecessary or actually detrimental, which are brought to the kidney by the blood. These are selected by

the kidney epithelium, some being passed, others retained, and yet others metabolized and passed in an altered state. The state of the kidney at any given moment is thus of great importance. The composition of the urine is an indication of the state of the blood, the accuracy of this indication being sometimes lessened by a diseased state of the kidney.

Disorders of Excretion.—These may be considered under the heads of (1) excretion of urine normal in composition but abnormal in quantity; (2) the excretion in abnormal amounts of substances normally present in the urine, and (3) the excretion of substances not normally found in the urine. Such a division, however, is hardly physiologically accurate, because the amount of urine is affected by its concentration in the matter of certain salts, so that divisions (1) and (2) may overlap.

Increased Amount of Urine, Polyuria.—According to general principles this may be brought about by (1) increase in the general arterial pressure without renal change, or (2) dilatation of renal arterioles without, of necessity, any rise in general blood pressure. (3) To these it is obvious that a third factor has to be added, namely, the effect of certain salts and other substances upon the secretory epithelium, stimulating it to greater activity. Diuretics may act in any of these three ways, and some of them in different ways at different times, or even in more than one of these ways at the same time.

Decreased Amount of Urine, Oliguria, or Anuria.—Reduction of urinary flow may be caused by (1) lowering of general blood pressure, (2) direct contraction of the afferent vessels, or (3) increased venous pressure; two of these may be included in the more general statement that a reduction in the difference between arterial and venous pressure leads to oliguria. To be added to these is (4) any obstruction to the urinary outflow, provided it affects both kidneys. The oliguria that is so marked a feature of acute nephritis is probably due to the amount of glomerulitis that is present, rather than to the effect of swelling of the epithelium and consequent diminution of the tubular lumen, although this is often pronounced and cannot be wholly neglected.

The Solids in Urine.—Some of these are the product of the ordinary processes of digestion and assimilation; some are the product of normal metabolic processes, others of abnormal metabolic processes; some are due to extraneous agents, such as bacteria or metallic poisons. The following is a list of the more important substances found in the urine, some of them only in minute quantity: acetone, achroglycogen, allantoin, carbamic acid, chlorides, cholesterin, chondroitin, creatin (?), creatinin, diacetic acid, diastatic ferments, glucose, hematoporphyrin, indican, isomaltose, lactose, mucin, nucleinic acid, nucleoalbumin, orthocresol, oxalic acid, oxaluric acid, paracresol, paraoxyphenylacetic acid, paraoxyphenylpropionic acid, phosphates, pentose, pigments, proteolytic ferments, ptomaines, purin bases (?), pyrocatechin, sulphates, urea, uric acid, and volatile fatty acids.

Urea.—The excretion of urea depends on (1) the ingestion of nitrogenous foods, and (2) the breaking down of the organized albumin of the body. The amount eliminated in the urine of a healthy individual on a mixed diet varies from 20 to 45 grams daily. The quantity is increased in febrile diseases and decreased in malnutrition, as well as in disease of the kidney parenchyma.

Uric Acid.—The daily excretion of uric acid in the healthy adult varies from 0.2 to 1.25 grams, and is derived from the katabolism of the nucleins in the food or the body tissues, so that whenever there is a loss of tissue albumin, as in fevers, its amount is increased.

Creatinin.—The daily excretion of creatinin varies from 0.6 to 1.3 grams, derived from a diet of meat or from the muscular tissue of the body. It is increased by bodily exercise and in fevers, and is diminished in many diseases that produce a cachectic state.

Albumin.—Various proteins may appear in the urine unchanged from absorbed food, as egg-albumin after an excessive diet of raw eggs, or as mucins or nucleo-albumins from tissue disintegration; but these are infrequent and unimportant compared with serum albumin and serum globulin, which are the bodies concerned when we speak of albuminuria. They are the dominant proteins of the blood plasma, and their presence in the plasma indicates an abnormal escape. Proof exists that the albumin escapes through the glomeruli, but it is also likely that when the tubular epithelium is disintegrating the albumin so derived is added; further, when the tubular epithelium is cast off, the naked basement membrane probably allows lymph to exude into the tubules. Thus, in a severe acute nephritis, it is likely that the tubules contribute a considerable amount of albumin, while in the milder cases the glomeruli allow the albumin to escape. The disintegration of cells is not necessarily accompanied by the presence of albumin in the urine. The albumin found in urine is usually serum albumin, but it may be globulin alone, or with mere traces of serum albumin. Since albumin is present in the blood plasma in a constant ratio to globulin of 3 to 2, and globulins are the more diffusible, these facts seem to indicate that the glomeruli have a power of selection.

"Physiological" Albuminuria.—This is the term used to designate the appearance of albumin in the urine in those whose subsequent history leads us to suppose that there is not any lesion existing to account for it. It may appear after cold baths or violent exercise, especially if the latter be performed soon after change from the supine to the erect posture.

Cyclical Albuminuria.—This is noted in the young; the morning urine is free from albumin, but it appears increasingly in the forenoon and disappears in the afternoon. The erect, active state may here again be a dominant factor.

Albuminuria from Circulatory Disturbance.—Whatever slows the rate of blood flow through the kidneys favors the appearance of albuminuria. Thus, contraction of the renal arteries, as in lead poisoning, or

various obstructions, as in heart disease, or in local obstruction of the renal vein, causes albuminuria with lessening of the amount of urine.

Toxic Albuminuria.—Many mineral and bacterial poisons, and the yet unknown toxin of eclampsia, are capable of causing albuminuria, chiefly by the damage wrought in the epithelium, although the glomeruli also are considered to be involved.

Infectious Albuminuria.—This is exemplified by scarlet fever and streptococcus infections, and is especially due to lesion of the glomeruli, with abundant discharge of albumin, and sometimes even of blood corpuscles; the parenchyma, too, is generally damaged.

Albumoses.—Albumoses appear in the urine when the intracellular katabolism of proteins is perverted, as in tuberculosis, suppuration, phosphorus poisoning and osteomalacia. **Bence-Jones' albumin** is a related form found in cases of multiple myelomas.

Hematuria.—Blood may appear in the urine from causes in the kidney or elsewhere in the tract; it may be evidenced by a dark or bright red color, and verified by the microscope, the spectroscope or by chemical reactions.

Hemoglobinuria.—Hemoglobin dissolved in the urine may appear when hemolysis has occurred, the material being actually secreted and not filtered in a mechanical way.

Disturbances of the Function of Urination.—The pelvis of the kidney and the ureters are merely amplified conductors of the urine. The bladder is a reservoir with functional power of discharge. The disorders of the conducting apparatus are, therefore, chiefly obstructive, and obstruction may arise in a variety of ways; it may result from (1) objects in the lumina, as calculi, tumors, clot, necrotic tissue, parasites and from sharp "kinks" in the tube; (2) thickening of the walls, as inflammations, neoplasms, and hyperplasias; (3) pressure from outside, as by tumors, exudates, organs misplaced, traction or pressure of fibrous bands, ligatures and so on. Finally, the same ultimate result may arise from a solution of continuity of the tube, so that extravasation of urine occurs. The effect of the various obstructions depends upon whether one or both kidneys are concerned; moderate obstructions may be corrected by hypertrophy above the point of obstruction and the correction of the diminution of urine by the employment of more force. But this cannot go on indefinitely; the extreme of hypertrophy is reached, further dilatation ensues, and the disability is aggravated. Stagnation of the urine, and subsequent infection thus results, and such an infection may progress upward to the kidney itself. Apart from such infection, the presence of the distending fluid acts so as to enlarge the pelvis with compression and atrophy of the kidney substance until the kidney becomes a large sac, in the walls of which the glomeruli and tubules still functionate. The pressure, acting upon the tubules, leads them to resorb fluid, and the pressure of these swollen cells, added to the general intramural pressure, lessens the flow of blood through the kidney,

diminishing the amount of urine secreted. If this state of affairs be unilateral, the other kidney may compensate entirely for the lack; but if bilateral, uremia and death may quickly ensue.

The bladder is specially concerned in regulating the function of urination. Were it not for the bladder, the urine would be continually escaping; but it acts as a reservoir and at the proper time a mechanism for evacuation. Functionally, it consists of two elements, a sphincter muscle which detains, and a detrusor muscle which expels the urine; the action of both being governed by the nervous system. In infants urination is reflex, being set in motion by peripheral impulses, chiefly the condition of distension of the bladder. Later, by education, the child is able to control and time the function. There is, therefore, a reflex centre (situated in the sympathetic system, not in the lumbar cord) and a cerebral centre. The sphincter, largely of voluntary muscle, relaxes and allows the membranous urethra to fill with urine, and the impulse becomes irresistible, the detrusor expelling the contents of the bladder. Factors which govern the reflex irritability are the amount of distension, the state of the mucosa, and the character of the urine. An inflamed bladder or a highly acid urine may initiate evacuation, apart from any marked degree of distension.

Retention of Urine.—Retention of urine may arise, apart from physical obstruction, from lack of peripheral stimuli, where, for example, the sensory nerves conduct badly or fail to conduct the message despatched by a distended bladder, or from a paralysis of the detrusor muscle, or from a spasm of the sphincter, or from loss of the mental control, as happens in acute fevers. When the distension of the bladder is so great as to overcome the sphincter, urination may occur until the excess is removed, the bladder still remaining moderately full. This is the "overflow of distension" and its occurrence at intervals may fail to warn the attendant that the bladder is never being emptied at all. Overdistension, too, may induce inability of the bladder muscle to contract. One variety of this is very important, viz., the local distension of the lower part of the bladder behind an enlarged prostate. The weight of retained urine and the weakness of the muscle allow the wall to sag and emptying of the bladder becomes impossible; the retained urine readily becomes infected, and allows the progress of inflammation and the formation of calculi.

Incontinence of Urine.—Incontinence of urine is the inability to retain it in the bladder. Apart from the incontinence of retention referred to above, this may arise from paralysis or weakness of the sphincter, or spasmodic overaction of the detrusor. The former arises from traumatism as in labor, or the pressure of tumors, while the latter is usually due to irritation of the mucosa.

Hydronephrosis.—When the outflowing urine is blocked by something which interferes with the discharging urine from the pelvis of the kidney, such as new growth in the bladder blocking the ureter, stone, inflammation, or a kink in the ureter, the kidney continues to secrete,

and the pelvis dilates gradually because the urine secreted into it is unable to escape, and as the urine increases the kidney tissue is pressed upon until it becomes very thin; a hydronephrotic sac may come to contain several liters of clear fluid, of low specific gravity, containing usually a little urea, rarely albumin. It sometimes happens that a hydronephrosis due to a kink in the ureter discharges itself at intervals, the very increase in size in some way "undoing" the kink. The kidney tissue may become narrowed by pressure to a mere shell, and the whole sac may attain a diameter that is incredibly large; the distension of the abdomen from hydronephrosis may simulate ascites. If unilateral, the condition may be borne for a considerable time; if bilateral, uremia intervenes.

Nocturnal Enuresis.—Nocturnal enuresis, or "bed-wetting," usually found in young children, is due to the excessive response of an unstable nervous system to some peripheral stimulus, such as intestinal worms in the rectum, phimosis, preputial adhesions, and many other such states. It may also be due, though rarely, to the occurrence of nocturnal epileptic attacks.

The Influence of Bodily States on the Production of Kidney Lesions. —The chief factor in the production of kidney lesions is the blood. On the one hand there are conditions leading to a diminished supply of blood to the kidneys, such as arteriosclerosis or a weak heart muscle, and others causing an increased retention of blood in the organs, such as obstruction, general or local. In both these groups, albuminuria is likely to supervene. Both groups, too, have this in common, that there is a deficient amount of nutrition supplied to the cells, and an imperfect removal of the toxic products of metabolism. Epithelium of the tubules and the glomeruli is likewise sensitive to such influences. The vasomotor influences, also, are not without effect; a marked deviation from the normal in the quantity of blood, especially if suddenly produced and frequently repeated, impairs the vitality of the organ, and paves the way for infection or other damage.

Even more important is the quality of the blood; it may be vitiated by the toxins of bacteria or by chemical poisons; bacteria may gain entrance to the kidney or may damage it by their toxins produced elsewhere in the body. Even the products of putrefaction in the bowel may be potent causes of trouble. Substances that are normally excreted by the skin, the lungs, or the liver may be thrown upon the kidney in states of incompetency of those organs. Finally, the kidneys may be damaged by the action of substances the result of perverted metabolism, such as appears to occur in eclampsia, diabetes, myxœdema, and other ill-understood states.

While we group many of these diseased states under the general heading of **nephritis** it must be remembered that we have two different orders of phenomena—**degenerative** and **inflammatory**. The former are manifested by retrogressive changes, such as cloudy swelling, fatty degeneration, vacuolation, and necrosis of the secreting cells, the latter

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by congestion, exudation, and hyperplasia of connective tissue. We are prepared, also, for the coexistence of these factors.

The Influence of Kidney Lesions on the Excretion of Urine.—Circulatory disturbances and other abnormalities thus affect the secreting structures; lesions of these structures, in turn, modify the composition of the urine, and the systemic metabolism. The urine is thus a reflection of the state of the kidneys and of the metabolic processes of the body; we therefore find in it deviations from normal in point of quantity, specific gravity, and reaction; in the appearance in it of abnormal substances such as albumin, blood cells, pus, epithelium, casts, blood pigment, salts, and bacteria; and deviations, too, in the amount of chemical constituents. These can be referred to only in a very general way.

Acute Parenchymatous Nephritis.—The amount of urine is greatly reduced; the specific gravity is correspondingly high, and because of concentration any abnormal constituents, such as casts, are not so far to seek as usual. The specific gravity may be 1025 or 1030, the urine is turbid, generally deeply colored. It contains a large amount of albumin, and much sediment, which consists of blood cells, leukocytes, renal and vesical epithelium, crystals of uric acid and oxalates, and casts of any or all sorts, especially epithelial. Its freezing point (determined by the process of **cryoscopy**) is higher than that of normal urine. In the form known as hemorrhagic nephritis, blood is present in considerable quantity. In acute infective nephritis, where bacteria are actually at work in the kidney the urine will be practically the same as in hemorrhagic (non-infective) nephritis.

Chronic Interstitial Nephritis.—In this form of nephritis the urine is greatly increased in amount, acid, pale in color, of low specific gravity (1002 to 1015). Albumin is present in small amount or may even be absent. Casts are few, and the solids generally diminished.

Pyelonephritis.—Cellular debris, urinary salts, epithelium, and pus are generally present; the blood of a free hemorrhage may appear in the urine; if there is ulceration, shreds of tissue also may be seen. The causative bacteria may be demonstrated in the urine. The excretion of salts, following Van Noorden, is thus: in acute nephritis and in acute exacerbations of chronic nephritis, urea, creatinin, pigments, hippuric acid, phosphates and inorganic sulphates are excreted with difficulty; water with even greater difficulty; uric acid, xanthin bases, aromatic substances, ammonia, chlorides and carbonates with ease. The nitrogenous elements in the urine are derived from the disintegration of proteins, and follow the same rules as in health. In a general way their excretion is parallel with the excretion of water.

The Relation of Kidney Affections to General Metabolism and the State of Other Organs.—It has long been known that nephritis is accompanied by lesions of other organs, for example, hypertrophy of the heart and high blood pressure. For long, the idea was current that the heart had to work harder to propel blood through the kidneys, but it is probably more correct to suppose that the toxic influences which

are responsible for the nephritis are also to blame for the stimulation wrought upon the circulatory system. It has long been said, too, that when the waste products of metabolism are not eliminated by the kidneys, they are vicariously excreted by other parts of the body, by purging, sweating and other modes. This again is not entirely borne out by experimental facts; true it is, clinically, that such methods of treatment in part are the most satisfactory we know. Nevertheless, very little urea can be excreted by the skin; and the possibility exists of concentrating the toxic materials in the body by the plentiful escape of water by the skin, so that uremia may be induced. The ulcerations that are prone to occur in the intestinal tract in nephritis are probably due to ammonia from the urea excreted into the tract, assisted by increased bacterial activity.

Uremia.—The symptom complex known as uremia consists of headache, dizziness, gastro-intestinal irritation, grave disturbance of the nervous system indicated by convulsions or coma, accompanied by high blood pressure and cardiac hypertrophy. Its cause is not yet known; the toxic effect of all the known urinary substances combined is scarcely sufficient to account for it. Perhaps, first of all, it is cumulative, and so the toxic effects quickly produced by experiment are not strictly parallel. Perhaps, too, the affected tissues have a special power in fixing certain toxins. The work of the ductless glands in these states is not yet sufficiently known.

Very important, clinically, is the fact that the retention of toxic substances, not excreted by the kidneys, leads to depression of the general vitality, so that the subjects of such retention are liable to succumb to infections of all sorts.

THE KIDNEY

Congenital Abnormalities.—**Absence** of both kidneys is not consistent with life, but absence of one has been seen in our own autopsy experience eight times. It is said, however, that in such cases careful examination of the connective tissue will reveal some trace of kidney tissue. Absence of the kidney has no bearing upon the adrenal of the same side, but is often accompanied by absence or anomaly of the genital structures. The ureter may be absent or a blind ureter may open into the bladder. The surgical importance of **unilateral kidney** lies in the rule that before removing a kidney the presence of the other kidney must be verified; the writer recalls an occasion on which observance of this rule prevented the surgeon from removing the only kidney.

Anomalies of Shape.—In unilateral absence of the kidney, the single kidney present is generally larger than usual, and often misshapen. Even when both are present one may be large, the other small. Anomalies of shape are often accompanied by anomalies of position (the brim of the pelvis being a frequent site), and nearly always by some unusual arrangement of the arteries and veins. Fusion of the two kidneys,

usually at the lower end, gives the **horseshoe kidney**; and a very common and quite unimportant anomaly is the persistence of the **fœtal lobulation** of the organ. Clinically important is the undue **mobility** of the kidney, which ranges from that observed in an organ that sags slightly, to that seen in a kidney which may be felt in any part of the abdomen. The amount of retroperitoneal fat surrounding it has an important bearing on the fixity of the organ. The congenital cystic kidney has been referred to elsewhere, especially with regard to its causation (p. 408); such a kidney possesses a number of thin-walled cysts, often reinforced by fibrous tissue and containing limpid fluid. They may be found quite late in life.

Congenital cystic kidney. Section showing multiple cysts affecting both cortex and medulla. (McGill Path. Mus.)

Circulatory Disturbances.—Anemia.—Anemia of the kidney may be part of a general anemia affecting all organs or may arise from something that prevents ingress of blood to the organ. The result of a sudden anemia may be anuria, and a sudden anemia from spasm of the renal artery is supposed to be the cause of hysterical anuria. As a result of long-continued anemia, epithelial degenerations ensue.

Hyperemia.—Hyperemia results from inflammation, or as a result of a general or local venous stasis. With an incompetent heart and a weak arterial flow, there is at first cortical and glomerular congestion with the appearance of albumin in the urine, and subsequently degenerations. The kidney is large, firm, and red; its capsule strips readily, its stellate veins are injected, its cut surface is bloody, and its glomeruli prominent. This hyperemic state, if long continued, leads to "**cyanotic induration**," and a well-marked fibrosis results. The secretion of such a kidney is scanty, of high specific gravity, with albumin and casts—a state of affairs that cannot easily be differentiated clinically from a toxic or other nephritis; in fact, as we have stated before, there is little or no need for such differentiation, for circulatory disturbances can cause nephritis in the ordinary sense of the term.

Thrombosis.—The arteries or the veins of the kidney may be thrombosed, most often as part of the manifestations of a terminal infection.

If death does not ensue, and the collateral circulation is at all adequate, the result will be practically a passive hyperemia.

Embolism.—Embolism of the renal artery results in rapid necrosis; of a branch of that artery, in infarct; if the embolus be infective, abscess results; if not, the familiar yellow or golden triangular infarct is seen; at times, as in eclampsia, the superficial part of the cortex appears as if infarcted in its entirety. Except in the case of the largest infarcts, there may be no sign or symptom other than the appearance of blood or hemoglobin in the urine and temporary rise of temperature; an infarct heals with the formation of a depressed scar on the surface of the kidney.

Fig. 346

Anemic infarct of cortex of kidney to show coagulation necrosis, with surrounding zone of congestion; *a*, artery. (Orth.)

Inflammation.—We shall consider under this heading the lesions that are designated as nephritis, with the caution that in many cases the changes are largely degenerative, that degenerative changes are sure to accompany an infective lesion, and that a chronic nephritis in which the changes are mainly degenerative may have arisen from an infective beginning.

It may be said that union of the observation of the clinician and the pathologist is necessary for the understanding of any disease; it seems as if the pathologists had "overclassified" nephritis, just as the clinicians

have overclassified the cirrhoses of the liver. The charge of incompleteness may be made against the classification which follows. It seems as if nephritis, clinically, could be divided into acute interstitial, acute parenchymatous, chronic interstitial, and chronic parenchymatous forms.

Fig. 347
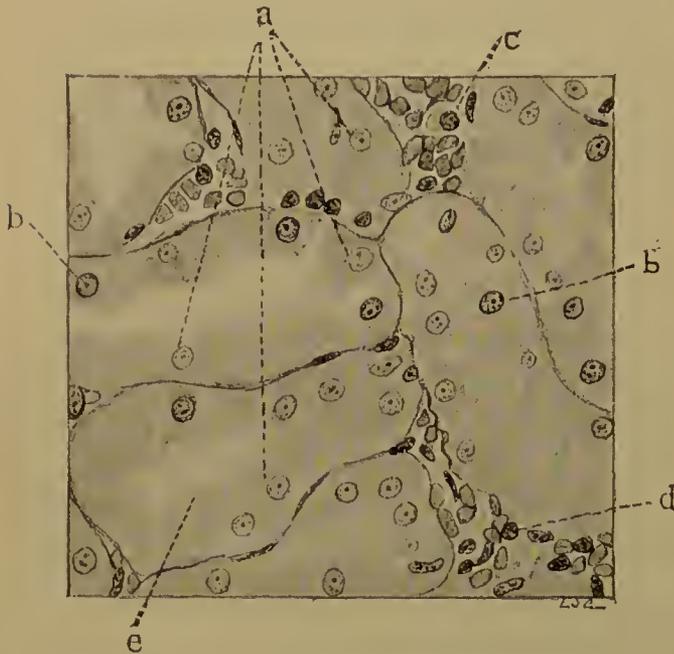
Early stage of acute parenchymatous nephritis, with marked cloudy swelling. Cell bodies are cloudy with beginning dissociation. Note variation in nuclear stain: *a*, pale staining nuclei; *b*, deeply staining; *c*, *d*, intertubular capillary; *e*, cell with pale or invisible nucleus.

Fig. 348
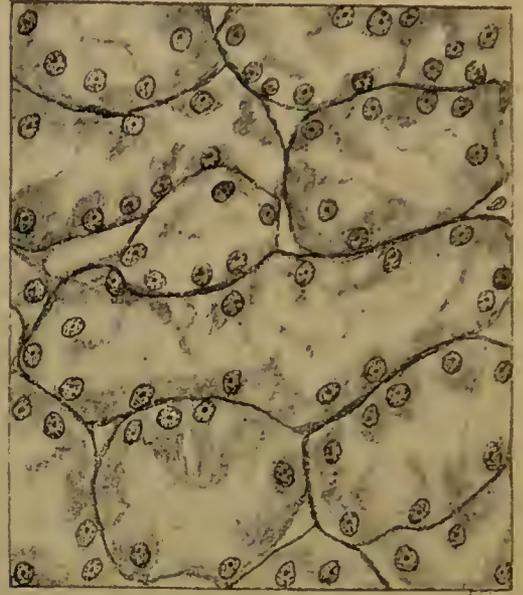
Acute parenchymatous nephritis, later stage with more acute disintegration of the cell bodies into the lumen.

Fig. 349
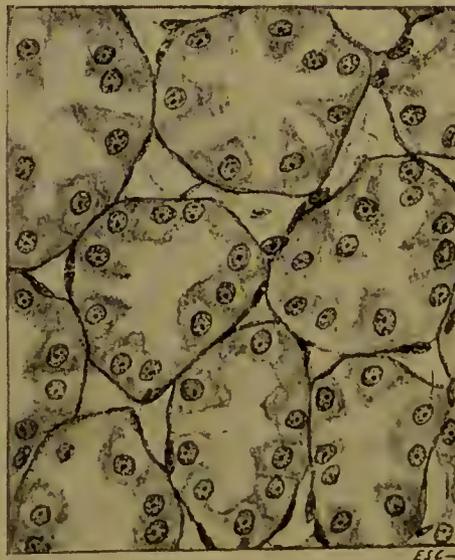
Acute parenchymatous nephritis, fully developed. A characteristic group of convoluted tubules showing enlarged stellate lumina, cells irregular with some multiplication.

Of these, all but the first are called Bright's disease; in the first, exudative changes are the most prominent, in the last three, degenerative. In the first, the bacteria are in the kidney itself, while in the last three the changes are mainly degenerative, due to toxemia, although not

entirely so, because, apart from their presence as a causative factor, bacteria may gain entrance as a secondary or a terminal infection. Acute interstitial nephritis is exemplified by the case of a kidney, affected, like other organs, in bacteriemia; acute parenchymatous nephritis by a kidney suddenly attacked and made to degenerate by a diffusible toxin, as in diphtheria; chronic interstitial nephritis by the kidney that is small, shrunken, damaged by numerous attacks of either of the foregoing, and chronic parenchymatous nephritis by the large, swollen kidney of many alcoholics. In indicating the characters of chronic parenchymatous and chronic interstitial nephritis, one might say that no case of a chronic kidney lesion can exemplify the one or the other purely; parenchymatous and interstitial changes are seen side by side, and it is not possible for any considerable degree of one to exist with-

Fig 350
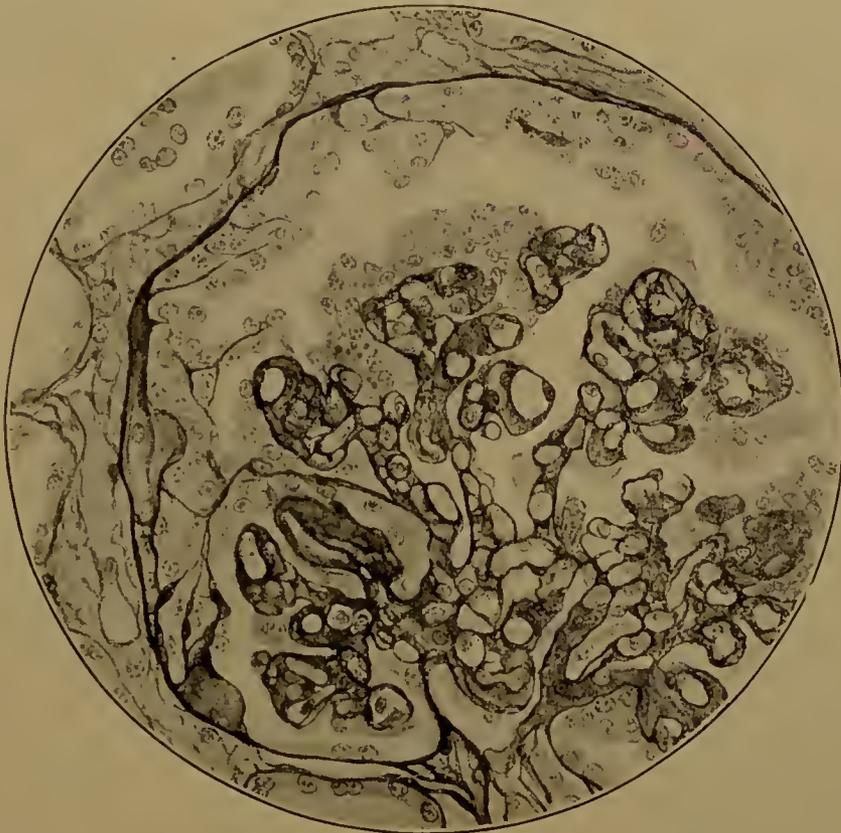
Glomerulus in advanced "glomerulonephritis," showing hyaline change in capillary walls and in the membrane of Bowman's capsule. The spaces in the tuft are cross-sections of the capillary channel. There is considerable proliferation of the lining cells of Bowman's capsule. (Harvey.)

out the other. There are two extremes between which lie all the cases; on the one hand, a kidney with marked fibrosis as the most prominent feature, and on the other, one in which a maximum degree of parenchymatous change is allied with little fibrosis.

The conditions that are essentially non-infective will be dealt with first.

Acute Parenchymatous Nephritis.—This is known as acute Bright's disease and is the state induced by a diffusible toxin such as is liberated

in the infectious diseases. The slightest grade is a state of cloudy swelling; in fact it is immaterial whether the term cloudy swelling or the term parenchymatous nephritis be used. The most extreme grade is that in which the kidney tubules are necrosed, their nuclei killed, and their function arrested all at once by an overwhelming force of toxin; in this state, there may be no changes wrought in the outward shape of the tubule and the glomerulus, no distortion, but the affected tubules are seen in a stained specimen without nuclei or other sign of molecular life.

Fig. 351

Section from a case of parenchymatous nephritis to show the (regenerated and modified) flattened epithelium lining the dilated convoluted tubules. As indicated by the loosened and desquamated cells in the central tubule the inflammatory process is here still continuing.

In general, the kidney is enlarged and may be œdematous, the cortex is pale, the stellate veins injected, and the lobules distinct; the capsule strips readily, and on section the cortex springs up, released from pressure, so that it stands higher than the medulla, the cut edge at the capsule everting and appearing rounded. The generally pale cortex

Fig. 352
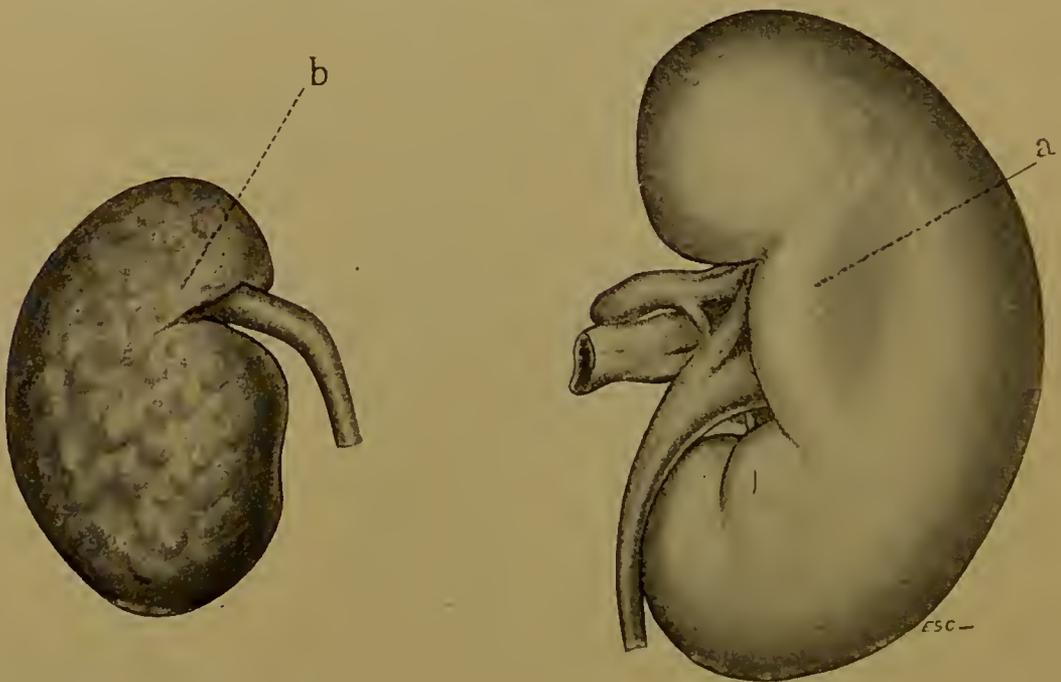
Large white (*a*) and small granular, contracted kidneys (*b*) (one-half natural size), to show relative size.

contrasts with the darker-red medulla, and sometimes minute hemorrhages can be seen in its substance.

Microscopically, all grades of damage are to be seen from cloudy swelling of the tubular cells with some encroachment upon the lumen

to a state of necrosis of entire tubules, glomeruli and all; or merely one part of a tubule may show no nuclei and the rest be in a state of cloudy swelling. In the tubules, especially low down, may be seen cells or casts; in Bowman's capsule the glomerular epithelium may be swollen and degenerated, and exudate may be seen in the space of the capsule. Especially in scarlet fever there may be a cellular migration into the glomerulus, a condition known as glomerulitis or glomerular nephritis. It does not appear necessary to class this form apart merely on this account. Hemorrhage may occur into the glomerular space, and blood and blood casts appear in the urine, warranting the use of the term **hemorrhagic nephritis.** Clearly such a series of lesions is the outcome of a diffuse toxemia, nor is this qualified by the fact that oftentimes one finds a cellular exudate in parts of such a kidney. The highly intoxicated organ is in a fit state to allow the admission of a secondary infection.

FIG. 353

Instead of dealing immediately with acute interstitial nephritis, which will be considered with other infective conditions proper of the kidney, the other forms of Bright's disease, *i. e.*, the chronic forms of nephritis, will be considered.

Chronic Parenchymatous Nephritis.— This form, called also chronic diffuse nephritis, is characterized by a large kidney, sometimes "**large white,**" sometimes "**large red,**" or even "**large mottled kidney.**" It may be merely a continuance of the acute parenchymatous state, or it may arise insidiously. Often the kidney of the alcoholic exhibits this variety of change. The dilatation of the cortical tubules is an important factor in the increased size of the organ. In

Chronic interstitial nephritis (small granular kidney). (McGill Path. Mus.)

addition while we distinguish here a certain implication of the interstitial tissue, it is notable that it is mainly in the form of a proliferation of connective tissue, and as fibroblasts are numerous we have here partly the cause of its increased size. It is in the state of enlargement, to be followed finally by contraction if the patient live long enough. The connective tissue of the kidney behaves as does the connective tissue of any other area in inflammation, passing first into a stage in which its bulk is increased, and subsequently to a stage in which its bulk is lessened by the contraction of fibrosis. It thus sometimes occurs that chronic parenchymatous nephritis is but an earlier stage of the so-called diffuse chronic interstitial nephritis.

The enlargement of the kidney gives it a plump look and if it be

held with the pelvis in the palm of the hand, its convex surface looks broad, somewhat square, and there may even be a kind of flattening along the convex border which reminds one of the longitudinal furrow over the spine of a fat hog, whence the name "hog-back" kidney. This somewhat quadrilateral shape may, however, be congenital. The bulky kidney is sometimes soft, although if congested it is firm, the capsule peels readily and leaves a smooth surface on which the veins are dilated and prominent. The prevailing color may be pale, or red, or mottled. On section the edge may evert, and the cortex is larger, deeper than normal, often pale and fatty looking; this fatty appearance is due to the presence not of free fat, but possibly of fatty soaps; anemia, too, has somewhat to do with it. Microscopically, the tubules differ widely. Some may be in a state of cloudy swelling with small lumina; others may show flattened epithelium with relatively and actually large lumina, the most characteristic type of change; others are so dilated as to suggest that they will subsequently give rise to the development of cysts. Fats or soaps or even myelin droplets may be seen in the cells, which tend often to be irregular, with ragged edges. Casts and debris may be seen in the tubules. Cellular infiltration may be noted in the interstitial tissue. In the glomeruli, albumin may coagulate in Bowman's capsule, or the debris of cells may be seen. The glomeruli are large, often lobulated, so that a glomerulus may seem to be cleft into two or three or more lobes. At other times the glomerulus seems to fill completely its space, and the lining of Bowman's capsule, instead of being one cell thick and scarcely discernible, may be a definite, easily distinguished line of perceptible thickness, the first indication of interstitial proliferation. There is some inclination to consider the large mottled kidney as differing in causation from the other forms mentioned, although its classification in this group is not invalidated. Löhlein and Gaskell find that it occurs characteristically with acute endocarditis, from which multiple emboli are lodged in the glomerular tufts with resulting local disturbance of circulation.

Chronic Interstitial Nephritis.—The above form may progress into this; or the interstitial form may, on the other hand, gradually arise in a kidney that at no time has been much larger than usual. Considering that there are various grades of involvement, a kidney typical of the advanced condition will be described. For such there are many names: granular kidney, contracted kidney, small white kidney, fibroid, cirrhotic or sclerotic kidney, or the kidney of indurative nephritis. There seem to be many different ways at least by which a kidney arrives at this state; as a sequel to parenchymatous nephritis, as a sequel to acute nephritis without the interposition of a stage in which the kidney is large, from arterio-sclerosis, from gout, from chemical poisons like lead, and as a result of old age. The kidney is small, hard, firmly elastic, resists the knife, and its outer surface is rough with small knobs of a few millimeters' diameter. When one attempts to remove the capsule, it comes away in many pieces after the exercise

of much pulling, and when it is being stripped one may see gradually breaking the tiny fibrous strands which have held it. The capsule itself may be much thickened. Cysts of various size, from those scarcely to be seen by the naked eye to those a centimeter in diameter, may jut from the surface or be opened by the cut; a clear fluid runs out of them. The pelvis looks large, and there is usually considerable fat lying in the connective tissue between it and the kidney substance, so that the kidney on section may prove to be yet smaller than it seemed.

Fig. 354
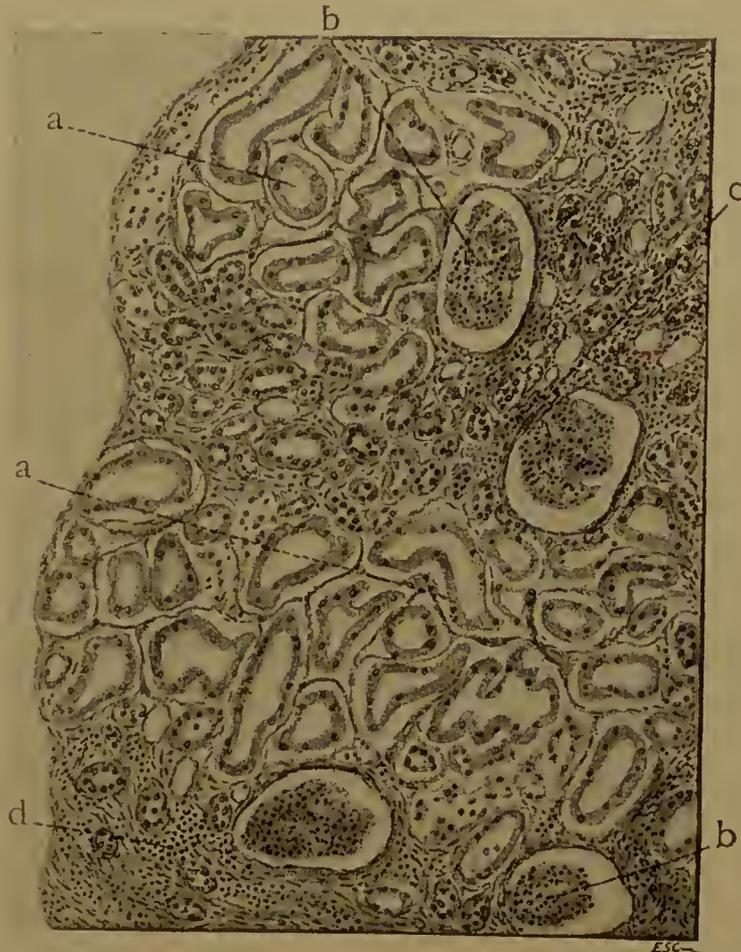
Section of cortex of kidney from a case of chronic interstitial nephritis (small granular kidney): *a, a,* areas presenting dilated tubules and hypertrophied glomeruli alternating with (*b*) fibrosed areas, *c, d,* atrophied tubules. The region selected does not show the hyaline contracted remains of glomeruli, usually observable in these areas. Note that the surface depressions correspond to the regions of fibrosis.

The cortex is often hardly distinguishable as such, and, when it can be distinguished, is narrowed to half its usual width or less; in the arterio-sclerotic form especially, its least and greatest widths differ widely. The color of cortex and medulla alike may be grey, red, mottled, or may exhibit any combination of these tints. On section, the tubules which in the normal kidney appear to touch one another are here separated by definite bands of fibrous tissue, which is often infiltrated by the cells of acute inflammation; in some parts of the field one may find almost entirely fibrosis, in others almost entirely tubules, and these

areas alternate, the fibrosis being greatest in the vicinity of an arteria recta. This alternation is especially characteristic of the arteriosclerotic form, whereas that following acute parenchymatous disturbance is apt to exhibit a more diffuse fibrosis. The tubules are often large, sometimes very large, and the epithelium may be flattened or absent; other tubules, less damaged, may still have an epithelium relatively so normal as to show cloudy, fatty, vacuolated, or other degeneration. The glomeruli are fewer than normal; some are large, partite, and active; others are represented merely by a round hyaline mass in which a few flattened nuclei are seen; these are evidently quite out of commission. On coördinating the gross and microscopic appearance, it is found that the granular surface is due to the effect of fibrosis; where a band of fibrous tissue has pulled in the capsule, a depression exists on the surface, and the knobs are the projection of masses of tissue not pulled in by the fibrosis (see Fig. 354). If such a kidney have sufficient tubules left, it may show the gross signs of cloudy swelling, but too often there are not enough for this, and the cut edge remains flat and well-defined, without any eversion of the edge. One is struck by the large amount of urine that can be secreted by such a damaged kidney.

Fig. 355

Section from a case of acute scarlatinal nephritis: convoluted tubules showing acute parenchymatous together with acute interstitial nephritis, evidenced by the plasma cell infiltration *a, a,* between the tubules.

Acute Interstitial Nephritis.—In this and the related infective, septic, and suppurative conditions we have to consider a twofold circumstance: (1) that we find in greater or less degree the results of the toxins acting in some of the ways we have just considered, and (2) that there is active inflammation following infection of the kidney tissue itself. Before proceeding to the infective states proper of the kidney, the reader may be reminded that in cases of infectious disease such as scarlet fever, there is an interstitial exudation of marked degree, but we would rather consider this as a fortuitous modification of a (primarily) parenchymatous nephritis than give the impression that Bright's disease has an acute interstitial type peculiar to it.

Infection reaches the kidney through the blood, or from the ureter and pelvis up the tubules, or more rarely directly from without, as from a wound, or equally rarely by extension from a nearby structure.

In a stage earlier than that of suppuration, a kidney so infected will show cellular infiltration of the type familiar in acute inflammation, and an accompanying cloudy swelling of the tubules. Such consti-

tutes the not-often-seen typical picture of acute interstitial nephritis. It is in the more advanced forms that we shall consider it, as these are so much more important practically.

The source of the infection, whether from the blood or by way of the tubules makes some difference in the distribution of the abscesses. In the former case the kidney is infected, like other organs, by the bacteria in the blood; actual emboli may be the form in which they are carried. This is especially noticeable as was previously stated in cases of vegetative endocarditis, and here actual small infarcts or areas of necrosis involve portions of the glomeruli. Both kidneys are involved, and the sites of infection are scattered apparently at random; if suppuration has not occurred, hyperemic areas with mottling may indicate the spots where the inflammation is progressive; if suppuration has occurred, the cut surface shows small multiple abscesses, which may appear on the surface

Fig. 356
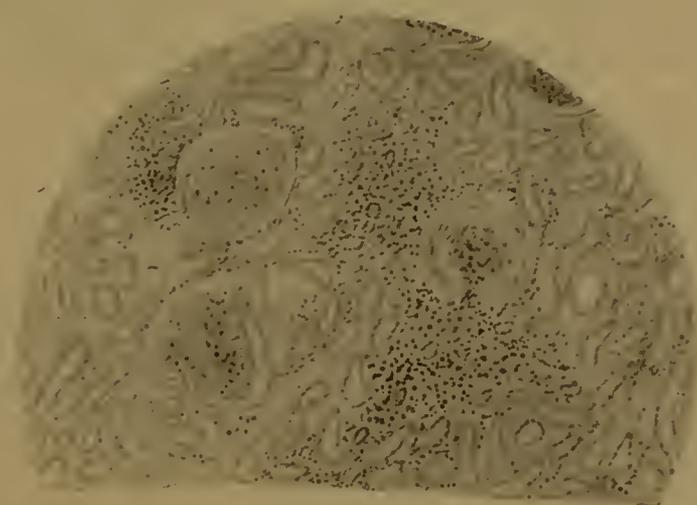
Recurrent interstitial nephritis (isolation of S. viridans at autopsy). Note that the dark dots represent cellular (mostly leucocytic) infiltration. Low power. (Prof. Oskar Klotz.)

also; when the capsule is stripped, these golden-yellow areas show well against the reddened background. The abscesses in the papillary part of the kidney may be elongated, indicating that in this direction the pus found least resistance; elsewhere they are usually round. In an ascending infection from the pelvis, the abscesses tend to be linear or to be arranged in groups that are linear, following the course of radii from the tip of a pyramid to the cortex; in a section of the whole kidney, abscesses may be seen arranged along such radii, but not continuously so, parts of the tubule that have served for the conduction of the infection being spared. At present there is a tendency to think that this linear arrangement is by no means so certain a proof of ascending infection as was thought. Microscopically, the abscess presents nothing that need be here detailed; the surrounding tissue may show œdema, and degrees of infiltration varying according to the distance from the abscess; the parenchyma is likely to be affected as much from

the general systemic toxemia as from the proximity of the abscess; by this is meant that if a tubule near an abscess be in a state of cloudy swelling it may have been rendered so by toxins that have come originally from this or another abscess and traversed the circulation before reaching the tubule.

Such a condition of the kidney tissue is usually called suppurative nephritis, in older phrascology "surgical kidney"; in the case in which it is caused by an ascending infection the pelvis must have been first affected (**pyelitis**), so that as soon as the kidney has become involved we may speak of a **pyelonephritis**; should the abscesses become large, so that the kidney is converted into a sac full of pus, the condition is called **pyonephrosis**. Should the abscesses remain small and encapsulated, healing may ensue. On the other hand, the infection may spread to the tissues around the kidney with the ultimate formation of abscess in these connective tissues, the so-called **perinephric abscess**, often rather inaccurately called perinephritic abscess.

Before leaving the suppurative processes of the kidney, it may be said that the pyogenic cocci, the Bacillus coli, and the gonococcus are the most usual agents of infection, and that the presence of stone is not infrequently a predisposing cause; the sac in which the stone lies may readily become infected, and a **calculous pyonephrosis** be the result. On opening such a kidney, the sac wall is apt to be fairly thick, made of the compressed kidney tissue, fortified by the capsule; the inner wall is often smooth, and the calculus may be seen adapted in shape to the bed in which it lies; the pus may have no outlet, and in process of time may become inspissated or even calcified.

In the above paragraphs it may seem that the classification of nephritis has been reduced to terms too simple to be effective; it may be pointed out, however, that the great complexity of terms generally in use would never have arisen if there had been a well-understood relationship between clinical signs and pathological observations. The truth is that no such accurate correlation exists; the clinical observations are very often merely variations upon the old theme of albumin, casts, and œdema, while the pathological observations are bewilderingly diverse. In the present state of our knowledge it is not often safe to predict what kind of kidney is going to be found in any given case; anyone who has followed his cases to the autopsy table has found small granular kidneys where he expected large white kidneys, and normal looking kidneys where he expected small granular kidneys, and so on; little or no dependence is to be put upon the value of granular or hyaline casts as indicating differences of lesion; the urine examined is an infinitesimal fraction of that excreted; the amount of urine and the number of casts must vary according to the amount of the urine and the completeness of the centrifugalization; and the reparative process in the kidney may exceed our expectation. We have some admiration for a certain pathologist of eminence whose pathological diagnosis rests content with the simple statement that "the kidneys

indicate Bright's disease," without attempting any more elaborate refinement.

Tuberculosis.—Tuberculosis of the kidney may be part of a general infection or part, even the chief lesion, of an infection confined largely, if not entirely, to the genito-urinary system. It is theoretically possible that tuberculosis might be primary in the kidney, the bacilli having gained no foothold and having caused no permanent lesion at their place of entry. It is not likely, however, that such conditions obtain frequently; careful examination will usually reveal a latent or quietly active focus in some lymph node or elsewhere.

As part of a general miliary tuberculosis, the lesions in the kidney are seen as small hyperemic spots that on section are leukocytic or lymphocytic collections, or as larger greyish or white dots appearing through the substance and on the surface of the organ; early abscesses or small fibromas may be mistaken by the naked eye for tubercles. These last seem to arise oftener in connection with the intertubular tissue than with the glomeruli.

In localized tuberculosis of the genito-urinary tract, the involvement of the kidney is more extensive, the infection is often bilateral, usually unequally advanced on the two sides, and caseation readily occurs; the pelvis, if not primarily affected, quickly becomes so. Whether, in fact, the infection travels from bladder to kidney or from kidney to bladder is a debated point; a good many cases seem to be definitely the latter. The caseated masses may fuse until the entire kidney seems to be a series of compartments full of caseous or caseopurulent matter; between them septa
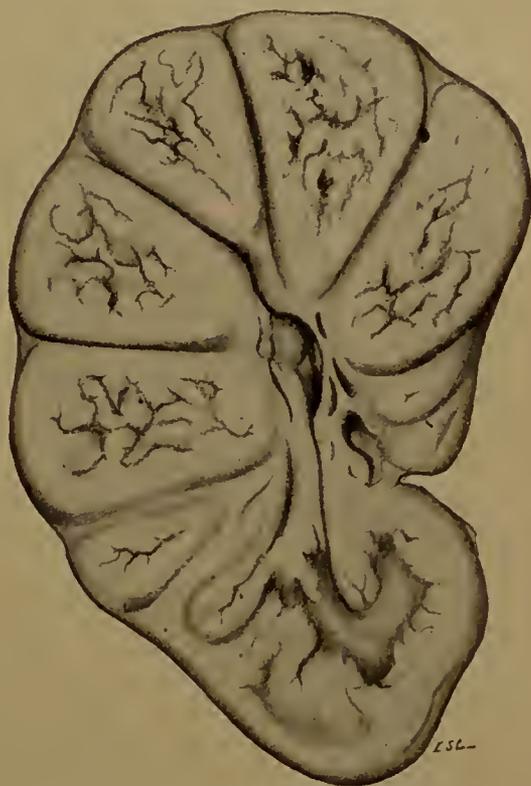
Fig. 357

Tuberculosis of kidney; one-half of the organ from a case of tuberculous pyonephrosis: the organ is converted into a series of sacs filled with brittle caseous matter. (McGill Path. Mus.)

run; half a dozen of such sacs may seem to fill the entire organ, including the pelvis, and the capsule, aided or not by a thin compressed layer of kidney tissue, may be the external covering (**tuberculous pyonephrosis**). Except in the case of the ureter becoming blocked or its walls gummed together, pus and at times blood will escape into the urine, and tubercle bacilli may be detected. This is, of course, possible only when the lesion becomes an "open" one, because in the case of thoroughly circumscribed caseous areas or of miliary tubercles, no way of escape is present. Much care has been taken with the detail necessary to determine tubercle bacilli in the urine; it is necessary to be sure that what

seem to be tubercle bacilli are not in reality smegma bacilli, which are acid-fast. The formamin method has simplified the search a good deal. It seems to be now generally conceded that no differential stain is infallible; the greatest care must be taken to wash the external orifices, to obtain the urine by catheter, and finally to use absolute alcohol as a decolorizer in addition to the ordinarily employed dilute mineral acid.

Syphilis.—Apart from the rare occurrence of gumma in the kidney, the recognition of syphilis in the kidney by any naked-eye lesion is a matter of great uncertainty. The kidney of the newborn is sometimes found affected, and the *Treponema pallidum* has been demonstrated. Even the picture of multiple scarring, which is attributed to syphilis, may be copied by lesions of a less specific nature.

Actinomycosis, glanders, and **leprosy** have been known to affect the kidney, but all are rare.

Regressive Tissue Changes.—**Atrophy.**—Apart from the atrophy of fibrosis which is a familiar picture, atrophy may be said to occur in marasmus and in senility, but it must be remembered that in the latter form the arterial changes of old age may be the cause. Atrophy from inactivity occurs in tubules whose glomeruli are damaged or congenitally imperfect. Pressure atrophy occurs in hydronephrosis, because the obstruction to the outflow of urine renders the intrarenal pressure high.

Cloudy Swelling.—It will be already clear that this results from toxins of many kinds. The cells are enlarged, of ground-glass appearance, and the lumen of the tubule is reduced in size. The best method of demonstrating cloudy swelling is to examine by the microscope a section cut by freezing, without preliminary treatment of any kind; the healthy tubules appear colorless, the tubules that are swollen are grey, and opaque; acetic acid clears them. In the stained section the lumen of the tubule may be stellate, and the staining power of the nucleus less than usual.

Fatty Degeneration.—This, like the previous change, which it follows, is seen to best advantage in the convoluted tubules. Fat droplets may be demonstrated by the use of Sudan III, the granules or droplets appearing golden or yellow.

Hyaline Degeneration.—This is to be seen in any section of advanced interstitial nephritis, the glomeruli appearing as round masses, smaller than normal. The hyaline cast is probably due to the change undergone by epithelial cells after they are shed, although occasionally coagulated albumin may form a cast of like appearance.

Vacuolar Degeneration.—Vacuoles may be seen in the epithelium of severely damaged tubules in nephritis, usually occupying the part of the cell nearest the lumen; the discharge of such vacuoles is thought to increase the albumin in the urine.

Amyloid.—This appears in the kidney as a deposit occurring first in the glomeruli, in cases of general amyloid deposit. The condition has nothing to do with the appearance of the waxy, so-called amyloid cast, which is probably a modification of the more frequently seen hyaline

cast. In advanced cases not only the glomeruli are amyloid, but the capillaries and the basement membranes of the tubules show the change. The vessel walls are thickened, transparent, and the lumina may be almost or entirely obliterated. In an advanced case, the cortex is greyish, in places translucent, and the glomeruli may be recognizable as grey dots, which react to the tests referred to in the paragraphs dealing with amyloid in general.

Pigments.—Pigments found in the kidney are derived from the blood or bile. Blood pigments may be laid down in any part of the kidney, appearing even in the secreting cells. Bile pigments lead to a diffuse or circumscribed greenish or yellow color, the secreting cells again readily becoming affected.

Uric Acid.—Reference has been made elsewhere (p. 284) to the ill-understood deposit of urates seen in the tips of the pyramids in infants at birth or shortly after; the salts are deposited in the lumina of the discharging tubules.

Progressive Tissue Changes.—Hypertrophy.—When one kidney is removed the remaining one grows larger by increase in the size of the glomeruli and the tubules; it is not certain that in the very young there is not an actual growth of new tubules, but such is unlikely. The younger the person, the greater is the capacity for hypertrophy.

Tumors.—It will be recalled that the mixed tumors of the kidney are of considerable importance and embryological interest (see p. 392). Apart from teratoblastomas, there are certain mesoblastic tumors to be considered of both hylic and lepidic types.

Fibromas.—These are small fibrous masses, appearing in the kidney, of whitish color, which are apt to be mistaken for miliary tubercles or even for abscesses. They are usually so small as to be barely distinguished by the eye, or may reach the size of a pinhead.

Lipomas, myomas, and **myxomas** are occasionally seen. The pure lipoma is usually small, but large ones have been reported, and they are to be distinguished from the "hypernephromas," which also may be very rich in fat. Most so-called myxomas are cases of myxomatous degeneration of some other form of tumor. The so-called **angioma** is probably always more correctly a **telangiectasis.**

Adenomas.—These vary in size from a millimeter in diameter to several centimeters, are single or multiple, soft and white. Histologically, they are solid or tubular, made of columnar cells, and the tubules may even be dilated into cysts. These adenomas are prone in later life to give rise to carcinoma, and both terms, considering the origin of the kidney, have to be used in their histological sense.

Carcinomas.—Carcinomas occur, developed from previous adenomas and otherwise; the diagnosis between adenoma and the malignant growth may be difficult to make, especially in those carcinomas arising from the tubular epithelium, as distinct from those of pelvic origin. The scirrhous, simple, and medullary types are found, the tumor being often of considerable size, but not attaining the bulk reached by the

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sareomas.   Prone to degeneration, hemorrhage is a likely occurrence. Secondary carcinomas are more common in the kidney than primary.

Sarcomas.—Endotheliomas, peritheliomas, and sarcomas of round and spindle cells are found in the kidney, both in youth and in adult life; the large tumors, supposedly of this nature, in the very young, often prove to be mixed (teratoid) tumors rather than pure sarcomas.

FIG. 358   FIG. 359
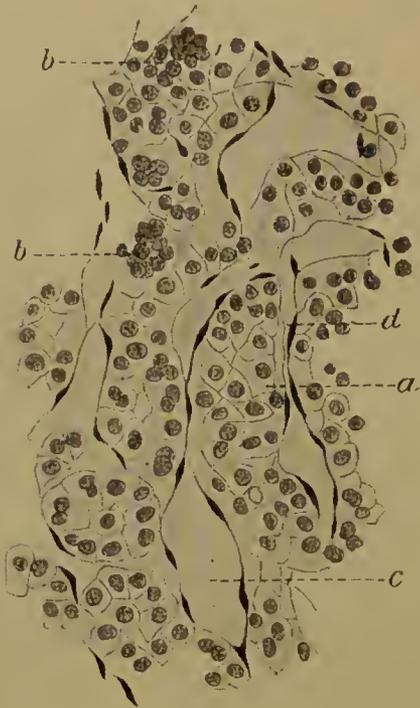
Section of a portion of a hypernephroma of the kidney. A characteristic area showing columns of clear polygonal cells, *a*, lying in immediate apposition to the endothelium (*d*) of the capillary sinuses (*c*). At *b*, areas of infiltration and degeneration.
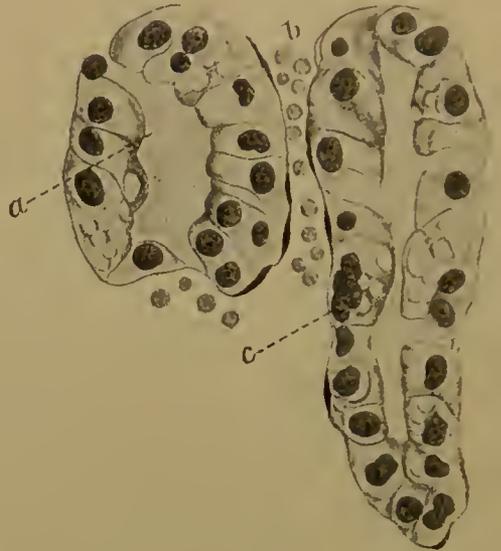
Section from another portion of the same tumor, more highly magnified, showing tubular arrangement: *a*, swollen translucent tumor cells surrounding a definite lumen. *b*, capillary: *c*, fat droplets in tumor cells. (Buday.)

Mixed Tumors (Teratoblastomas).—These are found at birth or shortly afterward. They are large, localized soft growths, prone to hemorrhage and to degeneration, and have been known by a great variety of names in which the sarcomatous nature is recognized. The growth consists of a sarcoma-like matrix in which there are epithelial elements, sometimes tubular, as well as fat, muscle, cartilage, and so on. They sometimes grow to a size truly enormous.

"Hypernephromas."—These, which we have elsewhere referred to as mesotheliomas (see p. 394), are masses of considerable size, circumscribed, and with a connective-tissue capsule, from which septa run into the mass of the tumor. The tumor is usually soft, yellowish, or brown, often red from hemorrhage and in some cases large collections of clot are found. The new growth pushes the kidney tissue before it, so that this may lie spread out upon the surface of the tumor. Metastases readily occur. Histologically, the tumor consists of a meshwork of capillaries, with

rows of cells variously arranged along them; the cells are often like those of the adrenal cortex, while in places they are arranged in masses and look like endothelial cells, which latter are in fact sometimes proliferated. Thus, a hypernephroma at one place may look like an angioma, at another like an endothelioma, or even like a sarcoma or carcinoma. The cells are usually polygonal, but may be cubical or columnar. An abundance of fat is sometimes seen in the cells.

Cysts.—Reference has already been made to congenital cystic kidney; retention cysts are very common, either as the comparatively small ones to be found in the kidney of interstitial nephritis or the larger ones that appear in otherwise fairly healthy kidneys of old people.

THE URETERS

Abnormalities.—The congenital anomalies of the ureters (and necessarily of the kidney pelves) have been considered with those of the kidney; the circulatory disturbances are of no moment, apart from their occurrence as accompaniments of more serious changes. Foreign body, particularly stone, is however, of much practical interest. Salts may be deposited in the pelvis of the kidney in the form of **gravel** or as the larger **calculi**, differing in size from the small particles that pass down the ureter without inconvenience, to large, coral-like masses that fill every crevice in the pelvis of the kidney. These are usually uric or uratic in nature, although exceptionally calcium carbonate and calcium phosphate are deposited. Lying in the pelvis of the kidney a stone may irritate the surrounding tissues and may after infection, become the centre of a calculous pyelitis, with irritative thickening of the walls of the pelvis —a state of affairs that soon allows the suppuration to spread to the kidney proper, with pyonephrosis, until ultimately a sac full of pus and calculi may be all of the organ that remains. It often happens that a stone or a piece of a stone leaves the pelvis and proceeds in the urinary stream down the ureter, where it is apt to be caught, either at the brim of the pelvis or just before the ureter enters the bladder. This gives rise to renal colic or more strictly **ureteral colic**, a very important complication of **nephrolithiasis**; the stone may be incapable of dislodgement, save by opening the ureter and removing it manually. Apart from calculi, blood clot, a piece of tissue, or of a tumor may act as a foreign body in the ureter. The ureter, serving as it does for conduction, is liable to have this function interfered with in various ways; **stenosis** may occur from general inflammatory or fibrous thickening of the wall, or from a local thickening acting as a valve. **Obstruction** may arise from the internal causes referred to above, as well as by pressure from outside, which may be exerted by a variety of objects, such as tumors, misplaced organs or masses of inflammatory exudate or inflamed tissues. **Kinks** may be produced in the ureter, especially when the kidney is unduly mobile, and the temporary blocking so produced may give rise to **hydronephrosis** .

Inflammation.—**Pyelitis.**—This most commonly results from an extension upward of infecting organisms from the bladder and urethra; it may occur by the infection of the ureter (**ureteritis**), the inflammation spreading by contiguity; or the infective agent of a cystitis or ureteritis of the lower end of the tube may be carried by the blood to one or both kidneys. Any interference with the outflow of urine tending to allow the urine to decompose increases the liability to such infection. More rarely, pyelitis and ureteritis occur by extension of a hematogenous infection of the kidney. The pyogenic cocci, bacillus coli, and gonococcus are all effective. A suppurative state of one kidney may readily infect the other by way of the ureters and bladder.

According to the severity of the infection, there may be merely a catarrhal state of the lining membrane of the pelvis, or the fluid exuded may be purulent, with or without the formation of a membrane; when stone is present, the irritant effect of the stone superadded may result in an ulcerative or even a gangrenous state of the wall. When the inflammation is of long duration, productive inflammatory overgrowths of papillate nature may be noticed. The ureter in its course can reproduce any or all of these states, although the complications due to the presence of a stone are infrequent, because the stone is not likely to remain at any one spot without precipitating the symptoms of obstruction. Finally, it is to be noted that in states of chronic inflammation of the pelvis and ureter formed masses of mucin may be thrown off by the surfaces, and their passage down to the bladder may be the occasion of attacks of ureteral colic.

Tuberculosis.—Miliary tubercles may be found in the pelvis or ureter in cases of generalized tuberculosis, but more often a localized caseous state of the pelvic wall follows tuberculous infection of the kidney. The wall becomes thickened, nodular, caseous tubercles coalesce, and the pelvic cavity becomes merely one compartment more of the multilocular caseous kidney (**tuberculous pyelonephrosis**). Perforation of the wall is provided against by the considerable thickening that it undergoes.

Parasites.—Parasites infesting the kidney, and, therefore, the pelvis and ureter, are not commonly found, but **echinococcus, cysticercus, filaria sanguinis,** and **eustrongylus gigas** may be mentioned among those that have been found.

Progressive Tissue Changes.—**Tumors.**—Tumors of the pelvis of the kidney and of the ureter are rare. Villous growths—**papilloma**—are the most common, and are apt to give origin to serious hemorrhage. **Sarcoma, carcinoma,** and **teratoma** are seen occasionally.

Cysts.—Following chronic inflammation, the wall of the pelvis or ureter (or even that of the bladder and urethra) may exhibit numerous small, pinhead cysts, containing watery, yellow, or even brown fluid. The trigone of the bladder shows the best examples. There is with these cysts some epithelial proliferation, and the condition is known as **pyelitis** or **ureteritis cystica.**

THE BLADDER

Congenital Anomalies.—The bladder may be **absent**, the ureters opening into the urethra, or the bladder and rectum may fail to be separated, forming a *cloaca*. **Septa** of the bladder may exist. **Extrophy** of the bladder, the most important anomaly, is seen when the two halves of the body have failed to unite along the median line; the posterior wall of the bladder lies open to the air, the pubic bones often lying separated by a considerable space. Frequently there is also with it epispadias. **Ectopia** consists of the extrusion of the bladder through a gap in the wall. The urachus may remain patent (**vesico-umbilical fistula**), or by imperfect closure **urachal cysts** may be caused.

Circulatory Disturbances.—**Hyperemia.**—Active hyperemia occurs as a stage of inflammation, and may exist without developing further, in cases where the urine is irritating, by reason of excessive acidity or the presence of certain chemical substances. Passive congestion, affecting especially the trigonal region, accompanies general systemic congestion; œdema is a frequent accompaniment. Hemorrhage in the form of petechiæ is seen in cases of cystitis, new growth, and those states in which it is found in the serous and mucous membranes. Hemorrhage in which much blood is effused is generally due to new growth or stone.

Inflammation.—**Cystitis.**—This occurs by extension of inflammation from the ureter or urethra, or as a result of abnormalities in the contents, viz., the presence of stone or decomposing urine. Rarely the infection is hematogenic. Of all these, the most potent cause is the retention of urine, the distended bladder being less resistant than the normal, and the chemical changes inducing the formation of substances that irritate the wall; in this state, a dirty catheter may introduce the organisms, or washing may wash back the urethral contents, or the blood may carry the necessary germs.

The urine is liable to undergo fermentation, alkalinity being produced by the action of the *micrococcus ureæ*. It is by no means necessary that the urine in cystitis be alkaline; indeed, numerous cases are now reported of cystitis, with acid urine, due to the bacillus coli.

Acute Cystitis.—**Catarrhal cystitis** is a comparatively mild affection, and it is notable that the bladder wall at autopsy may show no signs to the naked eye, although the existence of the inflammation before death was undoubted. The mucosa may be faintly reddened or swollen, especially around the trigone. A suppurative state, however, is readily observable. The mucosa is reddened, rugose, and if the urine has been alkaline, macerated. Patches of membrane, free or attached, areas of hemorrhage, the deposit of carbonates and phosphates, and a purulent exudate may be observed. The wall, on section, looks thick, œdematous and red, and actual abscesses may be seen in it (**phlegmonous cystitis**). Calcareous deposit is specially likely to occur on the ridges of the rugæ, while separation of the folds shows red, weeping furrows in which ulceration is usual.

Chronic Cystitis.—A slight acute cystitis may persist indefinitely and pass into chronic cystitis, as also may the severer forms. Sometimes the bladder is found distended, and sometimes contracted and rugose. As a result of the continuance of the infection, the mucosa and the rest of the wall tend to become hypertrophically thickened. The mucosa remains red, sometimes grey, often ulcerated, with incrustations of carbonates or phosphates.

Tuberculosis.—The most frequent mode of infection of the bladder by tuberculosis is by the passage of bacilli from the kidney; this is evidenced by the frequency with which a tuberculous ulceration of the bladder wall at a ureteral orifice is seen. Notwithstanding this, the healthy bladder wall can resist the attack of the bacilli for a considerable time, but a preëxisting cystitis of any degree will lessen this power. Prostatic tuberculosis is also able to infect the bladder. The disease is seen as miliary tubercles, each grey nodule surrounded by a small zone of hyperemia where the bladder is infected as part of a generalized tuberculosis, or occasionally where the bacteria from nearby sites have been well distributed in the urine, or by extension from a caseous focus in the bladder wall; more frequent is the localized caseous lesion, rapidly ulcerating. This arises by the coalescence of small tubercles, and tends to spread over the mucosa rather than deeply into the wall. The caseous material, constantly washed away by the urine, may not be evident, and the ulceration may be mistaken for a simple one.

Syphilis.—Gummas of the trigone have been observed, but syphilis of the bladder is very rare.

Bacteria and Parasites.—Bacteria are frequently found in the urine; the micrococcus ureæ seems to be a constant inhabitant of many healthy bladders. Pathogenic bacteria of all sorts are found, whether passed through a healthy kidney or not is debatable. Yeasts are found in the urine of diabetics, and sometimes of healthy persons. Among parasites, all those referred to as being found in the kidney, pelvis of the kidney, or ureter are naturally also found in the bladder, added to which are the eggs of *Bilharzia hematobium* escaping through the mucosa of the organ.

Abnormal Contents.—Blood corpuscles or pigments appear in the bladder urine in some cases of nephritis, in ulceration of the tract, in the hemorrhagic diseases and in cases where there is a neoplasm. Desquamated epithelium from the bladder or any higher part of the tract is seen, as well as casts of all kinds, and foreign bodies that have been introduced by the urethra. Lastly, calculi of various sorts are found. Uric acid, urate or oxalate stones may be passed down from the kidney, and may form the nucleus for phosphatic or other deposit. Foreign bodies or masses of epithelium may likewise form a nucleus for pure phosphatic stones.

Regressive Tissue Changes.—**Atrophy** of the bladder occurs in old age, as well as in some cases of advanced cachexia; the muscular tissue becomes greatly lessened, and the wall may be of extreme thinness.

Distension, long continued, is able to bring about the condition. The usual cellular degenerations are found in the mucosal cells; widespread necrosis usually occurs from trauma as in parturition or from the pressure of an unusually large calculus.

Progressive Tissue Changes.—Hypertrophy.—Hypertrophy of the bladder occurs frequently and forms one of the constantly-used examples by which "hypertrophy to overcome obstruction" is illustrated. It may result from obstruction, a real work hypertrophy, or may result from irritation of continued inflammation, as in cystitis, or in cases of vesical calculus. Even here, the constant mucosal irritation keeps

Epithelioma of the bladder infiltrating the muscle coat: *a, b,* cancer cells; *c,* muscle fibres: *d,* area with commencing invasion; *e, e,* connective tissue.

the muscle more or less constantly stimulated, so that work is also a feature in the production of this form. The bladder wall is thickened and firm; the trabeculæ are enlarged and prominent, and form a kind of basket-work on the inner surface of the bladder; the wall is thinner between the trabeculæ and in places becomes pouched out, giving rise to sacculations or even large diverticula; these are most apt to occur in the fundal half of the bladder.

Tumors.—New growths, both benign and malignant, are common in the bladder. The commonest is the **papilloma,** a soft velvety or villous mass attached by a pedicle to the wall. Usually red in color, these growths are very vascular, bleed readily, and necrose easily. Microscopically, the branches of such a tree-like tumor consist of a connective tissue core covered by stratified cubical or columnar cells. Some of these tumors become the seat of malignancy. **Fibromas** are

frequently seen, generally polypoid, and often becoming myxomatous. **Myomas, angiomas, adenomas** (probably arising from misplaced prostatic glands that sometimes exist in the wall) occur but infrequently.

Carcinoma is usually of the squamous-celled variety; these growths may be flat, nodular, prone to ulceration, whitish and fairly soft, or they may be papillary, cauliflower-like masses. **Sarcoma** is rarer than carcinoma, and presents no marked naked eye differences, save that perhaps the majority of cases of sarcoma show multiple growths. Secondary carcinoma of the bladder is quite common, in view of the liability of neighboring organs to the growth, viz., the prostate, the rectum, and the uterus, from which it extends.

Displacements of the bladder occur frequently in the female as an accompaniment of displacement of the uterus and other organs; the bladder has been found in hernial sacs, and we are acquainted with a case in which a diverticulum of the bladder was removed as part of the content of such a sac.

THE URETHRA

Congenital Anomalies.—The urethra may be **absent** in conjunction with other grave anomalies. It may open on the lower aspect of the penis (**hypospadias**) or on the upper side (**epispadias**); it may have more than one opening, or may open at the base of the scrotum or into the vagina. Obliteration or valvular obstruction of the urethra may occur.

Inflammation.—Urethritis.—This may arise by uncleanliness, from foreign bodies, from trauma, from calculi, or from the injection of antiseptic fluids, but of all cases of urethritis, overwhelmingly the most are due to the gonococcus. Gonorrhœal urethritis is more common in males than in females, because in the latter some other part of the tract is likely to be primarily infected; most frequently the disease is carried by coitus, although infection by means of infected towels or bed linen is possible. The gonococci in smears are apt to be in the pus cells, although they may be outside; it has been found in the conjunctiva, which is very liable to infection by the gonococcus, that when the pus fails to show the gonococcus, a light rubbing, not sufficient to redden the surface, will remove the superficial epithelial cells in which the gonococci are often abundant. This is not ordinarily mechanically possible in the urethra. When it is specially needed for diagnosis, cultures should be made; of late years with improved methods the gonococcus is grown much more easily than was formerly the case.

Early in the disease the surface of the urethra is reddened, with a catarrhal secretion which rapidly becomes purulent. Desquamation of the superficial cells follows, and sometimes ulceration, which may bleed, and the infection may spread backward to the prostate, and the bladder; in the female, the vagina may be affected throughout, and the uterus and tubes attacked; not infrequently the latter become diseased while the former escapes. In the female, Bartholin's glands are

certain to be infected; in all these out-of-the-way situations the infection may remain for a long time.

The inflammation may become chronic, and in the male, after the lapse of time, the secretion becomes scanty and less purulent, perhaps only cloudy or even clear to the naked eye (**gleet**). In the process of healing, the fibrous granulation tissue, if abundant, is apt to subside to fibrous masses or even bands, which impede the passage of urine (**stricture of the urethra**). Behind such bands and in irregularities of the surface, the gonococci may lurk for a long time, the urethritis disappearing in the meantime.

With a urethritis there may be considerable systemic intoxication; in the male the infection may attack the prepuce or go backward, causing epididymitis and orchitis; as a result of the constant stimulation of the mucosa, painful continued erection (**chordee**) may be induced. The nearby lymph nodes may suppurate (**bubo**), and **arthritis** by direct infection of the joints, and **tenosynovitis** may occur even at long periods after the acuteness of the infection has passed; general **bacteriemia**, and **endocarditis** are rare complications of the disease. Considering the frequency of gonorrhœa and the comparative unfamiliarity of the student and practitioner with the appearance of the urethra, it ought to be a part of every routine autopsy to remove and open at least the posterior part of the urethra. Strictures are of various kinds and forms, according to the situation of the ulceration or areas of ulceration that have healed.

Condylomas may be found in the urethra, usually at the meatus, as well as non-specific overgrowths of tissue.

Syphilis.—The chancre may be in the urethra, usually just within the meatus. Such infection may be coincident with that of gonorrhœa.

Tuberculosis.—Tuberculosis of the urethra is not common, being seen as miliary or caseous foci due to the spread of infection from other parts of the tract.

Foreign Bodies.—These are of necessity of the same order as those found in the bladder, but are not often found impacted in the passage.

Progressive Tissue Changes.—Primary **tumors** of the urethra are rare. In the female, a simple irritative hypertrophy of the mucosa may result in the formation of small fleshy excrescences—**caruncles**— which are extremely tender and bleed easily. **Fibroma** occasionally occurs as a polypoid mass. **Carcinoma** and **sarcoma** are rare, but may be present by extension.

Solution of Continuity.—The urethra may be lacerated or ruptured by violence, or by the passage of instruments, especially in the case of stricture, where the fibrous mass or band prevents the instrument from keeping the line of the urethra, and displaces the point of it laterally, where it impinges on weakened or even normal tissue, which gives way. The extravasation of urine that follows progresses into the tissues sometimes to an almost incredible distance, and constitutes a grave menace to life because of the certainty of infection in areas that are not easily reached by surgical means.

CHAPTER XII

THE REPRODUCTIVE SYSTEM

THE MALE SEXUAL ORGANS

THE PENIS

Congenital Anomalies.—The penis may be **absent, double,** or **hypo-plastic,** which last is found in cretins, cryptorchids, idiots, etc. The prepuce is rarely absent, but frequently **phimosed,** that is, the opening is abnormally narrow and the skin incapable of retraction. The important malformations of epi- and hypospadias have been considered with the urethra.

Circulatory Disturbances.—In valvular heart disease, the lax connective tissues of the penis are apt to be the seat of œdema, the corpora cavernosa becoming enlarged; the lax tissues of the prepuce may also exhibit great œdema. The sinuses of the corpora may become blocked, so that the corpora cannot be emptied, with the result that chronic congestion with erection (**priapism**) results. Bands, strings, or rings applied around the organ have caused gangrene by reason of the constriction and consequent great congestion. Hemorrhage may occur in the lax tissues of the corpora from trauma, with the formation of hematoma.

Inflammation.—Inflammation may attack the skin (**dermatitis**), the prepuce (**balanitis**), the glans (**posthitis**), or the corpora (**cavernitis**). Most commonly the prepuce and glans are attacked together (**balano-**

posthitis), the preputial sac being specially liable to inflammation from the tendency to accumulation of smegma, bacteria, pus, dirt and urinary salts. If the swelling of the parts be great, it may be impossible to draw the prepuce forward (**paraphimosis**). Ulceration and even gangrene may result; superficial erosions and subsequent adhesions of one layer of the prepuce to another, or induration and fibrosis are more frequent sequels. In cavernitis, the infection being closed in may lead to abscess formation, with subsequent rupture into the urethra, or a considerable induration in its healing. **Herpes progenitalis**, connected with the superficial nerves, arises as a group of small vesicles on the glans which rupture and form erosions.

Syphilis.—The primary lesion of syphilis, the **hard chancre**, is the most important affection, appearing three weeks or more after infection, upon the prepuce, near the raphe, on the corona, on the skin, or even

FIG. 361

From a section of a chancre of the prepuce at the twentieth day from its appearance. The indurating œdema corresponds to a distension and infiltration of the upper layers of the derma, which extends as a zone, *x, x, x,* about the centre of the chancre at *a*. The infiltration of the walls of the vessels is also well exhibited, especially at *b*. (Taylor.)

in the urethra. Beginning as a minute vesicle which may rupture, there is generally a small erosion surrounded by a reddish border, the whole being indurated. If picked up between the finger and thumb the structure feels bigger than it looks, as if a small piece of parchment underlay the inflamed spot. This sore is infective but does not infect a superposed layer of the prepuce, that is, is not auto-inoculable. Scrapings from it show spirochetes in large numbers. The lesion is so trifling in itself that it may be overlooked, but the most trifling lesion is almost sure to leave a definite scar. Microscopically are seen the signs of a low-grade inflammation; there is considerable infiltration by small round cells, especially around the vessels, a great deal of

proliferation of connective tissue, and giant cells may be present. By the time the chancre is evident, the infection has already become systemic, in evidence of which the inguinal gland is the first to show a considerable swelling, the **bubo** (called the **indolent bubo** from its slight tendency to suppuration).

At a later stage, the infection of syphilis, aided often by bacteria, causes an overgrowth of the mucosal elements of the vulva or anus, for example, the **condyloma**, which has a great tendency to ulceration; finally, gummas may be formed in any part of the penis, usually deep in its tissue, healing with much scarring; the formation of condyloma or gumma has no special relation to the site of the primary sore, and they are as likely to follow an extragenital primary infection as a genital one.

Chancroid.—Not at all to be confounded with the *chancre* or *hard chancre* or *hard sore* just described is the **chancroid** or **soft chancre** or **soft sore**, a non-syphilitic sore that frequently arises on the penis, caused by many different infective agents (though never by the treponema), ably assisted by uncleanliness. This arises from a few hours to a few days after infection, as a small vesicle or pustule which breaks down and forms a rapidly enlarging ulcer, with red, angry edges, and a moist, pus-secreting base, on which there may be a membrane. It is oftenest found on the prepuce or glans, and is auto-inoculable, so that the ulcers are often multiple; this, with the shorter incubation period and the more severe ulceration serve to distinguish it from the chancre, although it must be remembered that the two may coexist. A certain amount of induration may exist in the base of the chancroid, but it is not so well marked as in the chancre, where it persists after the inflammation has disappeared. A specific microörganism for the chancroid has been described, but it is generally considered that many common pathogenic organisms, some of which are certainly present in nearly all cases, are capable of producing the lesion. A chancroid may become infected with spirochetes, and the unobstrusive characters of the primary sore of syphilis be masked by the features of the chancroid, but the systemic infection will occur all the same. The chancroid may lead to severe balanitis, lymphangitis, suppuration of the inguinal glands (**virulent** as opposed to indolent, **bubo**), and the penis may even become phagedenic, phagedena being a rapid necrosis which is apt to affect those who are alcoholic, diabetic, syphilitic or otherwise greatly debilitated. **Tuberculosis** of the penis is rare, but has been met with in children as a result of the ritual practice of circumcision in cases where the saliva of the operator has contained bacilli. It is a notable fact that the smegma bacillus is in appearance and by some staining reactions very like the tubercle bacillus, and unusual care is therefore necessary in deciding whether or not tubercle bacilli are present in the urine.

Progressive Tissue Changes. — The Venereal Wart. — This outgrowth is inflammatory in its origin, but not necessarily venereal; the irritating discharge of gonorrhœa or other infection, together with uncleanliness, is sufficient to excite it. It consists of one or more papil-

lary excrescences, like a cock's comb on the gland or prepuce, sometimes flattened by the pressure of a tight prepuce, sometimes reaching a large size. Microscopically, each papilla consists of a fibrous vascular core covered by squamous epithelium, the core often branching so as to produce compound papillæ, and the squamous epithelium being at times so richly proliferated that a diagnosis from carcinoma is not easy. The mass is usually freely movable upon the subjacent tissue, unless ulceration has occurred. **Keratosis**, the outgrowth of a horny projection, similar to that seen on the skin, may occur. **Elephantiasis**, affecting chiefly the prepuce, is found; it may be combined with elephantiasis of the scrotum, and such a tumor weighing 25 kilos has been described. The mass consists chiefly of fibrous tissue and is of course the seat of marked inflammatory infiltration.

Tumors.—**Carcinoma** of the penis, generally of the squamous variety, has been found to compose nearly 3 per cent. of all cancers, so that its importance is considerable. Phimosis with the irritation of retained secretion seems to be a predisposing cause, while the warty and keratoid growths just described may form the starting point. The sulcus and the inner edge of the prepuce are the most frequent sites, where a small warty growth begins and spreads over the surface, forming a luxuriant mass that may erode through the prepuce; the numerous folds of the mass contain a foul, whitish, greasy secretion, and ulceration occurs readily, the surface becoming granular. The inguinal glands are naturally the earliest site of extension. Melanotic and other **sarcomas**, as well as **endotheliomas**, are found; secondary tumors are not common, while of the benign growths, **fibroma**, **lipoma**, and others are described. Sebaceous **cysts** of the prepuce and penile skin are encountered.

Injuries of Penis.—Injuries of the penis require a word of description; **luxation** may occur by the main substance of the organ being separated from the prepuce and overlying skin, so that it comes to lie beneath the skin of the trunk, the original covering hanging like an empty sausage skin. **Fracture**, chiefly rupture of the corpora cavernosa, occurred with some frequency when it was supposed by the ignorant that a chordee could be cured by violently "breaking the cord."

THE PROSTATE

Congenital Anomalies.—**Absence** of the prostate is combined with other grave defects of the genito-urinary system; aberrant and **unilaterally hypoplastic prostates** are exceptional; **cysts** along the course of the Müllerian duct are occasionally found.

Circulatory Disturbances.—**Hyperemia** is common, but unimportant. Very commonly a general dilatation of the veins of the prostatic plexus is seen, and **phleboliths** are common.

Inflammation.—**Prostatitis** is usually a sequel of gonorrhœal infection, but may result from cystitis or injury to the urethra. Beginning in the gland tubules, the infection soon spreads to the surrounding tissue, and multiple abscesses quickly result, which sometimes coalesce

to the almost entire destruction of the organ. Rupture of an abscess may happen into the bladder, urethra, scrotum, or perineum, and general peritonitis is exceptionally so initiated. Metastatic abscesses in bacteriemia are uncommon. **Chronic** prostatitis, of a less destructive grade, may result in considerable fibrosis, and in cystic dilatation of the tubules.

Tuberculosis of the prostate is fairly frequent, assuming the form of **multiple caseous nodules**, which may occupy the whole organ, causing much enlargement. The process begins in the tubules and is nearly always part of an extensive urogenital tuberculosis.

Foreign Bodies.—**Concretions,** the so-called "corpora amylacea," "amyloid bodies," "prostatic sand," "prostatic calculi," of one sort or another, are found in the prostates of a majority of elderly men.
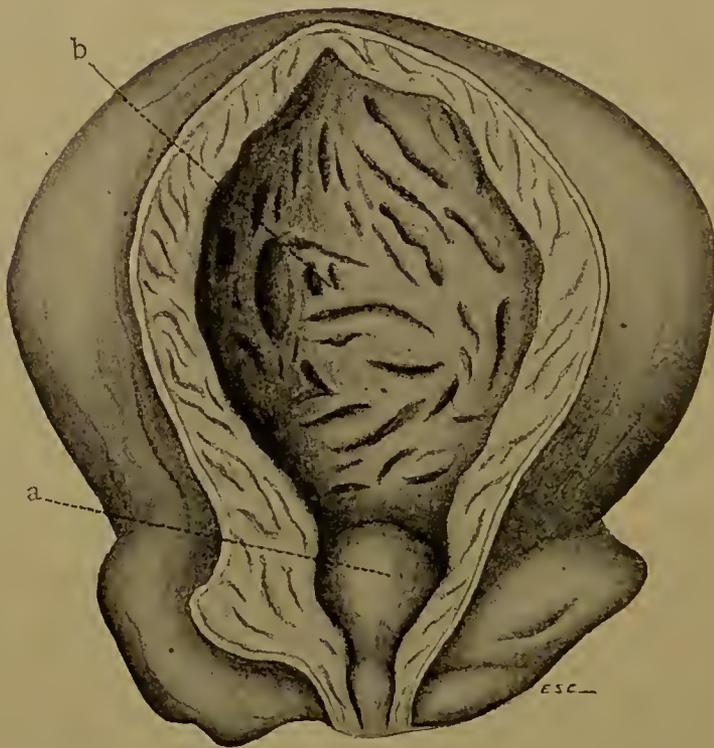
Hypertrophy of the bladder induced by hypertrophy of the middle lobe of the prostate, which, it will be seen, acted as a ball valve obstructing the orifice of the urethra: *a*, enlarged nodular middle lobe of prostate; *b*, greatly hypertrophied bladder wall.

They may appear to the naked eye like pepper grains, or they may be large and gritty like grape-seeds, when they are infiltrated with salts. Microscopically, the small ones are oval, round, or triangular, with concentric lamination, which gives them the appearance of starch granules, whence their name. Often, if not always, in normal or dilated tubes, they may be seen to commence from a fusion of desquamated cells which undergo hyaline degeneration. No lamination may be evident, the bodies being merely masses of brownish matter. The occurrence of corpora amylacea is of no practical significance, and has nothing to do with amyloid disease.

Regressive Tissue Changes.—**Atrophy** occurs in about one out of four old men, and in young people as a result of castration, wasting

disease, or the presence of concretions. In the last named the stroma suffers most, otherwise the glandular portion. **Fatty** and **hyaline degeneration** of the muscle fibres and of the epithelium are sometimes observed.

Progressive Tissue Change.—Hypertrophy.—The familiar enlargement of the prostate in elderly men, while it may precede malignant growth of the organ, is to be sharply distinguished from the same. The consensus of present-day opinion inclines to regard it as the outcome of a long-continued chronic inflammation of the urethral part of the organ; a constant relationship between previous gonorrhœa and prostatic hypertrophy cannot, however, be said to exist. Such a urethral inflammation may show itself in several ways:

FIG. 363
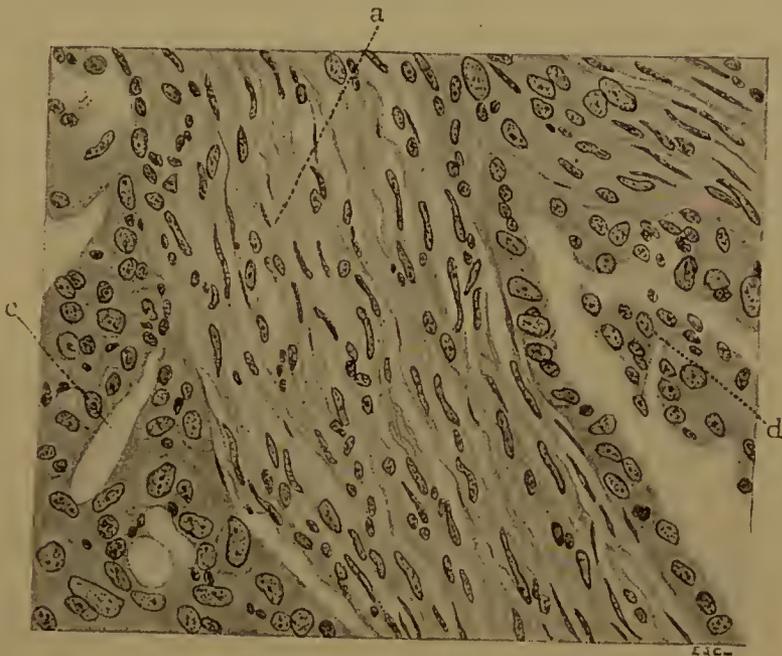
Section from adenocarcinoma of the prostate, showing on one side of the band of stroma (*a*), acini of relatively normal type (*d*), and on the other massive carcinomatous growth (*c*), with mere attempts at lumen formation.

1. Interstitial fibrosis around the mouths of the prostatic ducts may lead to partial obstruction, compensated by hypertrophy of the plain muscle fibres, giving a diffuse enlargement.

2. The fibrosis may give rise to complete stenosis of a duct, so that the associated glands become dilated and cystic—a condition often wrongly called cystadenoma.

3. Whether as a result of the preceding or from continued irritation, there may be active proliferation of the glandular epithelium, often with cystic dilatation.

4. Whether, again, from the progressive inflammation or as the outcome of loss of muscle fibres, with replacement by connective tissue, we may find a considerable diffuse hyperplasia of connective tissue combined with that of the muscle.

While the enlargement may be generalized, it often shows itself

specially in the middle lobe, where it brings about its most serious effects, for this nodule or ridge, projecting upward, acts as a valve when the bladder contracts, obstructs the orifice of the urethra and impedes urination; this leads to hypertrophy and subsequent dilatation of the bladder, and causes a bay or depression behind it in the lowest part of the bladder which fails to be emptied in micturition, and becomes an inevitable seat of bacterial growth, from which ascending inflammation, ureteritis, pyelitis, pyelonephritis, and pyonephrosis may result. The impeded urination calls for the employment of the catheter, a fertile source of infection, and the projecting mass of the prostate may even be pierced by the catheter, with the formation of a false passage.

The nature of the middle lobe of the prostate is not yet understood, for in the normal prostate of early life it is non-existent. By most it is regarded as an outgrowth from one or other lateral lobe.

Tumors.—Of malignant growths, **carcinoma** is the most important, occurring as a primary neoplasm, and not infrequently in a gland previously enlarged. We have observed one case in which urinary obstruction with enlarged prostate existed for eleven years before the development of an adenocarcinoma. Usually it is soft, nodular in one or both lobes, and spreading rapidly, it infiltrates the "capsule" of the gland, the mucosa of the bladder and the prostatic urethra, or may go through to the rectum. Microscopically, it consists of cylindrical or polyhedral cells, arranged in an attempt at glandular formation or in solid masses. Metastases are not a marked feature, and happen first in the retroperitoneal nodes, although in some cases there is a peculiar liability to form secondaries in the bones. **Sarcoma** is infrequent in comparison with carcinoma, but occurs in childhood, sometimes as one constituent of a mixed tumor. Secondary tumors rarely attack the prostate by metastasis, but may extend from the bladder or the rectum.

COWPER'S GLANDS

These small bodies, lying behind the bulb, are liable to **inflammation** by extension of processes that originate in the urethra, and rarely to **cyst** formation from blocking of the duct.

THE TUNICA VAGINALIS TESTIS

It will be remembered by the student that the testis, primarily in the abdominal cavity, descends into the scrotum along the inguinal canal. In this descent it pushes before it a prolongation of the peritoneum behind which it comes to lie, and along with this there is projected a portion of the muscular wall to form the *gubernaculum testis* together with associated vessels and nerves. Following this descent, the process of the peritoneum becomes normally closed off from the peritoneal cavity proper. Non-closure, with persistence of the inguinal

canal, favors subsequent hernia. The testis thus lies suspended behind a peritoneal sac, one wall of which, in juxtaposition to it, forms the visceral layer of the tunica vaginalis testis; the other, the parietal layer, is separated from the skin of the scrotum by loose tissue connective tissue, in which is the cremasteric muscle. The visceral and parietal layers enclose a serous sac, and this serous sac may show all the conditions seen in the other serosæ of the body.

Abnormalities.—In the preceding paragraphs we have already referred to these, viz., the patency of the neck of the sac.

Inflammation.—There may be a certain amount of anasarca of the tunica; of greater importance, however, are the collections of fluid resulting primarily from inflammation, viz., the condition of **hydrocele.** Here it is held that the first stage is a serous periorchitis resulting in distention of the sac by a clear serous fluid, and, once accumulated, the tendency to secrete fluid is maintained, so that tapping is often followed by reaccumulation. In more acute inflammation the fluid may be blood-stained and the exudate of a serofibrinous type with deposit of a membrane over the testis. In gonorrheal and traumatic cases there may be a **purulent periorchitis,** but acute periorchitis of a fibrinous type without marked fluid exudate may occur. It is not uncommon to find at autopsy old fibrous adhesions between the two walls of the sac indicating such old inflammation. Reverting to hydrocele, it deserves note that in a considerable proportion of cases no history can be obtained bearing upon any primary trauma or infection. Thus the etiology of the condition is not wholly worked out. In old collections, the hydrocele fluid may appear shimmering from numerous plates of cholesterine.

Syphilis and **tuberculosis** may involve the tunica by extension from the testis.

Progressive Changes.—Tumors primary or secondary, save by extension from the testis, are distinctly rare.

THE TESTES AND EPIDIDYMIDES

Congenital Abnormalities.—It will be remembered (Fig. 213, p. 408) that the epididymis and testis originate from two separate bodies, the former coming to constitute what may be termed the collecting tubules for the latter and that, owing to imperfection in the junction between the two parts, certain orders of cysts may develop. So also it may be recalled that in development, adrenal tissue may be snared off and carried down along with the descending testis. As regards the testis itself there may be various grades of lack of development or failure to attain the normal position in the scrotum. There thus may be absence of both testes or **anorchidism,** absence of one testis—**monorchidism,** non-descent into the inguinal canal—**cryptorchidism,** duplication of a testis—**polyorchidism,** or fusion of the two—**synorchidism.** **Hypoplasia** or incomplete development is met in cryptorchidism and

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other forms of **dystopia** or failure of the organ to pass into the scrotum; in cretinism and other cases of delayed or imperfect development. There may be various grades of dystopia, the testes being found in or near their primordial position in the neighborhood of the lumbar vertebræ, in the pelvis or imperfectly descended in the canal, or again, descent may be not into the scrotum, but into the tissues of the inside of the thigh. There may be not only congenital, but acquired dystopia, as occurs occasionally after trauma, the testis being forcibly displaced from its site, usually up the canal. Very rarely both testes have been found in the same half of the scrotum.

Aspermia.—Absence of discharge of spermatozoa in the adult may be due to (1) lack of production in the testis, or (2) to stenosis, obstruction or destruction of the vasa deferentia as the result of trauma, inflammation or new growth. Prolonged obstruction to discharge leads eventually to atrophy of the epithelium of the tubules of the testis, and so in certain cases both causes may be operative. Deficient production of spermatozoa, with consequent sterility may be brought about by many causes, some congenital, some acquired. Thus aspermia is encountered where the testes are retained in the abdominal cavity, even although apparently fully formed; for a few years around the age of twenty it is stated that such cryptorchids may present spermatozoa in the semen, but after the age of twenty-four they are uniformly found sterile. Imperfect development of the testes has also associated with it aspermia or oligospermia. Such hypoplasia is frequent in cretins accompanying defective development of the thyroid; in acromegalic giantism there is a similar aspermia and lack of sexual capacity. In the very obese, men and animals, aspermia shows itself, passing off with reduction of the obesity. General lowering of vitality as by long-continued disease and after excesses of various kinds, including mental worry and overstrain, leads also to lack of development of the spermatozoa.

To the contrasted condition of precocious sexual maturity we have already referred (p. 97).

Circulatory Disturbances.—The only serious circulatory disturbances are traumatic hemorrhage and the secondary effects of arrest of circulation as from thrombosis of the pampiniform plexus.

Inflammation.—Inflammation may be either ascending, along the vas deferens, in which case the epididymis is first affected, or hematogenous when the body of the testis is more liable to be involved. Most often both testis and epididymis are implicated. The most frequent form of inflammation is that due to the gonococcus, and here there is first a catarrhal epididymitis followed by a more interstitial orchitis. The epididymis becomes enlarged, tense, and painful, on section is found congested, showing tubules distended with semifluid exudate. At times this passes on to actual abscess formation. The testis similarly becomes firm and painful, and there is a similar catarrhal exudate in the tubules with an accompanying pronounced cellular infiltration

of the stroma. With arrest of the acute condition, fibrosis, shrinkage and atrophy of the organ may supervene, if the inflammation has been long continued. The type example of hematogenous orchitis is seen in mumps; at times this complicates other acute infections, *e. g.*, small-pox and typhoid.

Infective Granulomas.—Both tuberculosis and syphilis are apt to affect these organs. In tuberculosis, more often the infection is ascending and as a result the epididymis is apt to be the earlier and the more involved. The discovery of an enlarged epididymis may be the earliest clinical sign of the existence of tuberculosis in the body. There is formation of relatively large caseous masses with extensive destruction of the tissue of the organ and progressive extension of the process along the tubules into the testis. If the process reaches the tunica vaginalis adhesions may be set up with eventually ulceration of the skin and sinus formation.

In contrast to this the most frequent form of syphilitic implication involves the testis proper, as a diffuse fibrosis, the so-called white swelling. Less frequently definite gummas develop. In the former condition the testis becomes enlarged, hard, and insensitive to pressure. With the latter, as with tuberculosis, the skin may be involved and break down.

Regressive Changes.—Simple **atrophy** of the organ with aspermia is a senile change, and occurs in marasmus and wasting diseases, as also as the result of the influence of *x*-rays. Pressure atrophy is noted in conditions of hydrocele, hernia, and neoplastic growths.

Progressive Changes.—**Hyperplasia.**—Cases of precocious development and maturity of the testes have been noted particularly in connection with hypertrophy and tumor formation of the adrenal cortex. In the adult there is little evidence of **compensatory hypertrophy** after removal or destruction of one of the pair, though this may occur in the very young.

Tumors.—Tumors of the testis are not uncommon; they are characterized, as a group, by rapid growth and malignancy. The variety of forms described is bewildering. Recent careful studies of several sections from various areas in such tumors are leading to the conclusion that the majority are of teratomatous nature. Several cases are now on record of **chorio-epithelioma.** Very frequently we encounter mixed tumors with glandular, cartilaginous, sarcomatous, and other tissues. In addition we may find tumors of simple type; it seems that pure **sarcoma** may originate from the interstitial cells of the testis and that pure **carcinoma**, occurring as it does in adult life, may originate from the tubules of the organ. Other cases of so-called **carcinoma sarcomatodes** are explicable, when it is remembered that the testicular epithelium is of mesothelial origin, and that therefore, we would expect to find transitional **mesotheliomas.**

Cysts.—We have already referred to the congenital cysts, and it remains only to note the **spermatocele**, a relatively large cyst, originat-

ing apparently from aberrant tubules of the epididymis which, under the influence of some obstruction, may become of relatively great size extending into the cavity of the tunica vaginalis testis and simulating a hydrocele. This on puncture affords a fluid containing spermatozoa.

THE SCROTUM

The conditions affecting the scrotum are, broadly speaking, those liable to affect the skin in general, with certain modifications due to its position, and the relative abundance of its constituents. Thus the tunica dartos contains distinctly contractile cremasteric muscle fibres, and there is a lack of subcutaneous fat; it is peculiarly liable to be involved in **elephantiasis**, and then may attain a huge size. Its vascularity favors **hemorrhage** in trauma and in obstructive heart disease; in renal disease, **œdema** may be extreme. Of tumors the most important is **carcinoma** (squamous epithelioma), apparently secondary to irritation. In the old days chimney sweeps were peculiarly liable to this form of cancer, and today workers in tar and paraffin show a similar liability.

THE SPERMATIC CORD AND VESICULÆ SEMINALES

Especially in those having a long spermatic cord the accompanying veins of the pampiniform plexus are liable to varicosity, and as these are relatively abundant they may form a tumor-like mass, **varicocele**. This is found more frequently on the left side in consequence, it is held, of the course of the vein on that side, which renders it more liable to pressure and obstruction.

Inflammation of the vas deferens occurs, not as an isolated condition, but in association with epididymitis and vesiculitis; as a result there may be a reparative fibrosis leading to blockage of its lumen and consequent sterility. Regarding the vesiculæ seminales, there has been some debate as to whether these are to be regarded as reservoirs for the sperm or as affording a special secretion for admixture with the same. Apparently in man they have the double function. Inflammation in its active state may lead to marked tumefaction, and subsequently to fibrosis and contraction. As to its causation, the gonococcus is the most frequent infecting agent, though pure streptococcus infections also occur. **Tuberculosis**, both ascending and descending, may involve these and the vas.

THE FEMALE SEXUAL ORGANS

THE EXTERNAL GENITALIA

Abnormalities.—There is a long list of abnormalities of the external genitalia, involving either individual parts or the whole tract. Of the entire tract there may be complete absence as in certain monsters, hypoplasia as in cretinism and other forms of incomplete development. Of individual parts, the **vulva** may be abnormally small; the **clitoris** may be absent, or hyperplastic, as in some cases of false hermaphroditism, or doubled, as the lowest grade of inferior duplication, or adherent to neighboring structures. The **labia** may be abnormally small or abnormally large; the labia minora, as a congenital condition or as an acquirement, may be of great size (**Hottentot apron**). The labia majora, corresponding to the two halves of the scrotum, may at times possess a patent canal of Nuck, into which hernia occurs. Into such, there may be an imperfect descent of the ovary. The **hymen** is inconstant; it may be absent, even in the young child; may present an abnormally small orifice, may show all possible variations in the form of its orifice; may show multiple orifices, or lastly may be imperforate, in which case, with the onset of puberty, there develops retention of the menstrual blood.

Circulatory Disturbances.—There are certain important circulatory disturbances of the external genitalia, due to their vascularity. **Passive congestion** accompanies the later stages of pregnancy, and **œdema**, especially of the labia, may be very pronounced in general anasarcous states. **Hemorrhage** and **hematoma** are most frequently traumatic in origin.

Inflammation.—**Trauma**, inflicted in parturition and otherwise, is a common cause of transitory inflammation, especially in the labia; any part of these may be the site of laceration. Owing to the frequency of discharge from the vagina, and to urination, the external parts are apt to present irritation and infection, so that numerous **cutaneous disturbances** may show themselves here. Added to this must be considered the effects of friction upon surfaces so inflamed. Erysipelas, furunculosis, and milder infections causing erythema and eczema, are to be noted in addition to the important group of venereal infections. Apart from syphilis, these last include all the inflammations due directly to the gonococcus, and indirectly to the combination of uncleanliness with pathogenic bacteria, of which the chancroid, single or multiple, is a frequent result.

Acute vulvitis, generally associated with inflammation of the vagina, will be considered with that condition, but it requires mention here that in gonorrhea the glands of Bartholin are prone to an elective implication. In very young children, uncleanliness often leads to marked inflammation and excoriation, apart from vaginitis.

Infective Granulomas.—**Syphilis** may present itself in the form of the primary sore, the chancre, or of mucous patches, condylomas, of secondary eruptions, as again of gummas of the labia. Any part of the external genitalia is liable to be affected. **Tuberculosis** is rare, appearing occasionally as **lupus.**

Regressive Changes.—**Atrophy** occurs in the old. A remarkable condition known as **kraurosis vulvæ** is due to a fibrous hyperplasia of the subcutaneous tissue of the labia, with thinning and atrophy of the skin, and, being generalized, results in a progressive contraction of the vulvar orifice.

Progressive Changes.—As in the scrotum, so here there may be **elephantiasis** of one or both labia; hypertrophy of the labia minora and clitoris is considered as oftenest due to masturbation.

Tumors.—**Fibromas** of large size have been reported as originating in the clitoris and various parts of the vulva. **Nævi** and **angiomas** may be encountered, still more rarely **myomas, lipomas,** and **chondromas.** Perhaps the commonest tumor of this region, and even then not very frequent, is the **squamous-celled carcinoma. Melanotic sarcomas** have been reported. Among cystic formations, most common are retention **cysts of the glands of Bartholin.** A rare cyst, corresponding to scrotal hydrocele, may originate from the canal of Nuck.

THE VAGINA

The vaginal walls are normally in contact, rugose, except in the old and after frequent parturition, sparsely provided with glands, lined by squamous epithelium. Despite its simplicity of structure, the vagina partakes in many diseased conditions arising in its immediate neighbors, the external genitalia and the uterus. Its relations to nearby organs, the uterus, bladder, rectum, and the viscera in Douglas' pouch, favor alterations in position due to pressure or traction exerted upon it. The vaginal wall, having no inherent rigidity, is liable to become inverted, or even prolapsed through the vulvar orifice. Upon the vaginal space various organs may obtrude themselves; the bladder may descend as a mass in the vagina (**cystocele**); the rectum may push forward the posterior wall (**rectocele**), and loops of the bowel or even sometimes the ovaries may encroach upon the passage (**enterocele, ovariocele**). In parturition, and otherwise, the wall may be injured or completely torn. Foreign bodies in great variety have been encountered in the vagina, as, for example, forgotten tampons, pessaries, and objects introduced for purposes of masturbation. On one occasion we found at autopsy the lower half of a test-tube an inch in diameter firmly imbedded in the canal, where, to judge by the surrounding granulations, it had been for a considerable time. Such objects remaining for a long time usually become crusted by phosphates and carbonates.

Abnormalities.—The vagina may be **absent** or **duplicated**. More common than either of these states is a relative narrowing (atresia) which may exist at one or more points, or throughout the tube.

Circulatory Disturbances.—In the later weeks of pregnancy, **passive congestion** is noted. Hemorrhage in the walls is usually traumatic.

Inflammation.—**Vaginitis**, often associated with vulvitis as **vulvovaginitis** may be acute or chronic. Among acute infections, as might be supposed, gonorrhea is the commonest. An acute inflammation from gonococcus or other agents may spread from the vulva; the discharge of acrid or infective material from the uterus is also a cause. The wall is reddened, secretion is increased, and this, at first catarrhal, later becomes purulent. In young children vulvitis may spread to the vagina, in spite of the protective hymen, and it is worthy of note that accidental infection of infants by gonococcus may readily occur. In children's hospitals, a case of vulvovaginitis is so liable to infect the entire ward, that it must be cared for by an attendant who does not deal with the other children; this by reason of the intimate handling required for the cleanliness of infants.

Chronic vaginitis is an extremely important affection; it arises by continuance of an acute vaginitis, or may originate by a low form of infection in debilitated subjects, in whom it is liable to show slight exacerbations over a long-period (**leucorrhea**). The discharges of the uterus are here also of importance, in continuing the irritation. The local result is hypertrophy of the mucosa, which may appear granular or papillate, eventually, at times, atrophied and smooth. As a result of inflammation in nearby organs, as well as of trauma from within the vagina, **fistulæ** may be found, **rectovaginal**, or **vesicovaginal**.

It is noteworthy that the vagina rarely exhibits either tuberculous or syphilitic lesions.

Regressive Changes.—With age the rugæ of the vagina tend to disappear, and the wall to lose its velvety surface, becoming smooth.

Progressive Changes.—**Tumors.**—Tumors of the vagina are relatively uncommon; a form that is characteristic is the teratoblastomatous mixed tumor, encountered in children, presenting largely sarcomatous elements along with muscle cells and other connective tissues. Pure **sarcomas** have also been recorded, as have **leiomyomas**. The vagina may be the site of primary **squamous-celled carcinoma**, and secondaries are prone to infiltrate from carcinoma of the uterus, bladder, or rectum, as well as from **chorio-epithelioma** of the uterus.

THE UTERUS

The uterus is a thick-walled organ, pear-shaped, but flattened from before backward; it is composed of the myometrium formed, in the main, of plain muscle fibres, having a serous peritoneal covering over most of its extent, and a mucosa, the endometrium, consisting of columnar epithelium prolonged into the muscle as an abundant series of simple,

glandular acini. These glands are somewhat more elaborate and abundant in the cervical region. There is no sharply-defined submucosa, but immediately underlying the epithelium is a reticulated stroma characterized by a relatively abundant accumulation of cells, which, in passing we would note, must not be mistaken for an inflammatory infiltration, or for a diffuse sarcomatous growth. The inner layer of the myometrium is richly vascular, and in the multiparous woman these vessels show the evidences of involution and new formation with peripheral hyaline changes to which we have referred on p. 276. There are, further, abundant lymphatics, those of the cervix communicating with the iliac lymph nodes, those of the body of the organ with the lumbar and inguinal groups.

Abnormalities.—Of congenital abnormalities, mention may be made of complete **absence** and marked **hypoplasia**; the organ may be duplicated (**uterus didelphys**), with or without duplication of the vagina. Where the Müllerian ducts unite into a common cervix, the uterus is **bicornuate**; there may be two cavities enclosed in a common uterus (**uterus septus**). Considering the juxtaposition of uterus, bladder, and rectum and the primitive common cloaca, it is not remarkable that occasionally separation is imperfect with resultant **uterovesical** and **uterorectal** **fistulæ**. There may be **stenosis** of the cavity associated with imperfect development of the uterus along with that of the other genitalia.

Congenital Anomalies.—Two great classes of anomalies can be recognized: the **dystopias**, due to nutritive disorders, resulting in abnormality of size; and the **dysplasias**, due to eccentricities of development. They may be associated.

The uterus may be wanting (**aplasia**) or diminutive (**hypoplasia**), and this may be symmetrical or asymmetrical according as the Müllerian ducts, which form the organ, are equally or unequally involved. Transverse **fission** of the os uteri may be confounded with that resulting from childbirth. Real aplasia is rare, for nearly always some rudiments of uterine tissue are to be found. The external genitalia are generally intact, but the ovaries and tubes may occasionally be absent.

Where one Müllerian duct fails almost entirely to develop, the **uterus unicornis** is formed. If the ducts fail to fuse, **uterus didelphys** results, in which there are two separate uteri and vaginæ, or two uteri and one vagina. If the ducts fuse below, and not above, **uterus bicornis** results, and modifications of this are seen in **uterus bicornis duplex**, where there are two complete cavities; if these unite at the cervix we have **uterus bicornis unicollis**, while if a septum divides the uterine cavity, the condition is called **uterus septus** or **bilocularis**, and there are names to distinguish the various degrees of completeness of the septum.

The cavity of the uterus may be absent, or there may be multiple rudimentary cavities; it may be narrower than normal or obstructed (**stenosis uteri**), or it may be in communication with the bladder by a tube, or with the rectum (**congenital uterorectal fistula; anus uterinus**). The uterus may fail to develop beyond its fœtal state (**uterus fœtalis**)

or beyond its infantile state (**uterus infantilis**). On the other hand, it may develop precociously. Occasionally at birth the uterus is found **retroflexed**, in varying relation to the cervix, **retroverted**, or **anteflexed**. It has even been found in an inguinal or crural hernia (**uterocele, hysterocele**).

Acquired Abnormalities of the Uterus.—The pressure of tumors, fluid or organs misplaced, or traction in unusual directions or its own weight may misplace the uterus, and if it be mobile may even impart an abnormal shape to it. As a whole the uterus may be misplaced forward, backward, to the side, upward, downward (**prolapse**), or it may be turned inside out (**inversion**). Again, the same agents may bring about such pressure that there is an alteration in the direction of the axes of the uterus; it may be rotated in its transverse axis (**version**), usually backward (**retroversion**). This may exist in all degrees from a slight tilt to that in which the uterus lies with the fundus below the promontory of the sacrum and the cervix behind the symphysis pubis; these dislocations usually result from childbirth or abortion, where the increased weight of the uterus is not compensated by the fixity of its supports. Weakening of the round ligaments and, above all, the lack of perineal support after tears, are the most potent causes. A uterus so misplaced is prone to impairment of circulation and may become congested and enlarged, with the production of endometritis. Abnormal anteversion is not so liable to happen, and when it does, is usually from the traction of repaired tissue in front.

Inversion.—Inversion of the uterus occurs in a large lax uterus, such as may be seen after delivery. It may be (1) *incomplete*, with the fundus still within the uterus, or (2) *complete*, where the fundus lies in the vagina, or (3) *complete with prolapse*, where the uterus is wholly and the vagina partly everted, and the uterus appears outside the vulva, where interference with its circulation may lead to all degrees of degenerative change, even gangrene.

Prolapse.—In simple prolapse, the uterus descends and presents itself without inversion. It may lie in the vagina (*procidentia*) or with inversion of the vagina, may protrude through the vulvar orifice.

Several conditions may favor prolapse, chief of which is lack of support, whether from weakening of the ligaments or of the pelvic floor. Retroversion practically always precedes prolapse, and is assisted by injury to the pelvic floor, increased weight of the uterus, and laxity of the abdominal wall. The bladder or rectum or both may accompany the uterus in its descent. As in retroversion, but to a greater degree, there is interference with the circulation resulting in passive congestion and endometritis. Prolapse is necessarily accompanied by some displacement of the rectum or bladder or both.

Elevation.—Elevation of the uterus happens when it is pushed up from below by a tumor. When it gains attachment to the abdominal wall, so that involution cannot properly be accomplished, the result will probably be an elongation of the organ.

Flexion.—For long it has been the custom to speak of a class of abnormal conditions—flexions—in which the uterus becomes bent upon itself, giving **anteflexion, retroflexion,** and **lateral flexion,** but at present the tendency is to minimize the importance of this change, and to merge each of these in the more important *version* in the same direction. **Retroflexion** is the most common, associated, as it usually is, with retroversion, and if pregnancy occur the organ may be incarcerated in its new position, with abortion as a result. The causes of flexions are laxity of its tissue or its supports and undue tractions or pressure on one or another part of it.

Stenosis.—We have already referred to congenital stenosis: the acquired stenoses are usually due to contraction after curetting, or inflammation or obstruction of the channel by tumors. It may occur in pregnancy as a result of gonorrhœa.

Dilatation.—Anything that favors retention leads to distension of the uterine cavity with or without a corresponding hypertrophy of the uterine wall. As noted more than once previously, the extent of this hypertrophy is largely a matter of age. In the elderly there is little reactive overgrowth following the stress of distension. A very frequent cause of this is the continued growth of an intra-uterine fibromyoma which encroaches upon the cavity. In such cases the hypertrophy of the uterine wall may be remarkable. With imperforate hymen or cervical stenosis, there may be great distension from accumulation of menstrual fluid (**hematometra**). Retention occurring after the menopause or before puberty may result in the accumulation of clear fluid in the cavity (**hydrometra**). If the obstructed uterus become the seat of purulent inflammation, **pyometra** results. An infrequent condition is the accumulation of gas in the uterine cavity, seen occasionally in the puerperium when putrefaction of the retained lochia or placenta is present.

Rupture.—Laceration of the cervix is a common event in delivery, particularly in the primipara. The severer condition of rupture of the body of the organ may be brought about by any condition which leads to continued, strong uterine contractions without progression of labor, such as occurs where there is a transverse presentation. Here one may expect a longitudinal tearing of the uterine wall, slight or complete, with passage of the fœtus into the peritoneal cavity. Apart from the longitudinal, tears of all positions and degrees have been observed. Previous disease, with degeneration of the uterine wall, predisposes to these events.

Bruising and Perforation.—These occur in attempts at mechanical abortion, or during operative measures (curetting); dilatation by force is always a crushing or bruising. It must be remembered by the operator every time he takes a curette in hand that the most skilful of operators have perforated the uterus by the use of a force that could not be called other than gentle. In these cases, the perforation is usually at the fundus. Apart from these operative perforations, there may be

perforation resulting from cancerous and other deep ulcers, these often leading to the formation of utero-rectal, utero-vaginal and utero-vesical fistulæ.

Circulatory Disturbances. — Hyperemia. — Active **hyperemia** occurs physiologically every month during the period of sexual maturity of the unimpregnated female. Each menstrual period is immediately preceded by a phase of active congestion of the organ culminating in multiple hemorrhages in the hypertrophied mucosa, and casting off of the degenerated mucosal cells. Under pathological conditions, active hyperemia is found both where there is a local acute inflammation and as an accompaniment of general infections.

Hemorrhage.—Apart from menstrual hemorrhage of normal amount, there may be **menorrhagia,** an excessive loss of blood at the menstrual period. This may be brought about as a result of chronic passive congestion, predisposed to by the existence of uterine tumors, both benign and malignant, as well as by the presence of inflammation of the uterus or its appendages. **Metrorrhagia** is the escape from the uterus of blood which is not menstrual. This assumes its gravest diagnostic import in women who have passed the menopause, in whom its existence demands the suspicion of the presence of carcinoma of the uterus. Apart from this, it may occur as an accompaniment of general diseased states such as the hemorrhagic diseases, and severe general toxemias; more frequently it depends upon some local disorder which tends to congestion or ulceration (endometritis, new growths, etc.). **Hemorrhage,** not included in the above, occurs during and after parturition, in which cases an excessive amount depends generally upon imperfect contraction of the uterus, due either to an inherent failure of the muscle to perform its function or to the presence of retained placenta or tumor which constitutes a physical obstacle to complete contraction. In elderly women, associated with pronounced arteriosclerotic changes in the vessels of the organs, it is not very uncommon to have hemorrhage of a moderate grade in the mucosa, with some escape of blood into and out of the uterine cavity.

Inflammation. — Inflammation may affect the serous covering of the uterus and the structures intimately connected with it (**perimetritis** a local peritonitis), the surrounding pelvic organs, including the broad ligaments (**parametritis**), the uterine muscle (**metritis**) or the endometrium (**endometritis**).

Endometritis.—According to the region affected, so do we speak of **cervical endometritis** or **cervicitis, corporeal endometritis** of the body, or **general endometritis,** involving the entire uterine lining. The same grades of inflammation may occur here as are found in connection with any mucous membrane, although the warning must be given that very considerable experience is requisite before the histological appearances of the endometrium in certain stages of the menstrual cycle can be surely differentiated from those of inflammation. We recognize, for example, acute catarrhal endometritis, showing hyperemia with

discharge of an abundant viscid or in more advanced cases, a muco-purulent secretion; this latter constitutes **leucorrhea**, of which it may be said that, in the majority of cases, it is the cervix which is involved, and that we deal with a recurrent, often chronic catarrh. More acute disturbance leads to **hemorrhagic endometritis**. Acute endometritis arises from vaginal infection, not necessarily gonorrheal; more rarely it is of descending origin, and a degree of it may accompany a variety of disturbances of the adnexa, or of the uterus itself, especially if these are accompanied by a chronic congestion of the mucosa.

Chronic Endometritis.—This results most often from a combined catarrhal disturbance, and as in the stomach, for example, so here, on the one hand, there may be a distinctly productive or hyperplastic condition, sometimes even going on to the formation of nodular, polypoid, or papillate overgrowths of the mucosa; or, on the other hand, if the mucous membrane becomes exhausted, to atrophy with thinning of the endometrium. Here, again, as in the stomach, there may occasionally be inflammatory obstruction of the ducts with cystic dilatation of the same.

On microscopic examination, if the glands seem to be the seat of the most marked change, the state is called **glandular endometritis** in contradistinction to **interstitial** where the morbid changes in the interstitial tissue seem to predominate. Microscopic determination is difficult because of the changes incident to menstruation. The gland tubules are generally lengthened, tortuous and irregularly dilated even to the extent of cyst formation; the epithelial cells have lost their cilia, are clear, swollen, and mucoid. The lumina of the ducts are filled with mucus, leukocytes and desquamated cells, while the interstitial tissue is proliferated. The presence of the glands among the muscle bands must not be mistaken for malignancy, for it will be remembered that there is no submucosa.

Late in the disease the mucosa may become atrophic, smooth, thin, pigmented, and fibrous. The accompanying fibrosis is apt to compress some part of the tubules so that they dilate. Another result of irritation is the conversion of the mucosa into squamous epithelium; this seems to bear upon the occurrence of squamous carcinoma in the body of the uterus, but it is likewise to be remembered that islets of squamous epithelium have been discovered in the decidua, and even in the uteri of foetuses and infants.

Like the other forms of inflammation, chronic endometritis arises from various causes, a recapitulation of which would be to repeat what has already been said when dealing with the acute form.

In **chronic cervical endometritis** a frequent result is the formation of small cysts, which may attain the size of a pea, the so-called **ovula Nabothi**. They have usually clear, viscid contents. They are really retention cysts, due to erosion (wherein the proliferated epithelium "corks" the gland ducts), and are liable to infection, which may lead to abscess formation. Microscopically, the glands are seen to be

enlarged, with many cells converted into goblet cells; such cases are readily mistaken for carcinoma. As a rule in this form of endometritis there is abundant leucorrhœa.

As a result of injuries in labor, and secondary also to such chronic catarrh, the cervix is apt to show a series of disturbances. The external os appears no longer round, but transverse, and the extremities of this transverse slit are so deep as to constitute actual fissures, whose edges are red, often tumefied, the entire os sometimes appearing coated. The congested surface readily erodes and bleeds, and may show a variety of secondary changes, characteristic of progress or repair of the lesion. Therefore, we may find ulcerations, scars, cysts, granulations of normal extent or so exuberant as to suggest new growth, which indeed may follow this chronic inflammation.

Metritis.—Metritis is most frequently associated with the puerperal state, though it may be secondary to acute infection especially if associated with the trauma of operation. The uterine muscle takes on a pale color and a soft, friable consistence; accompanying it there may be acute hyperemia of the endometrium and occasional hemorrhages within the muscle substance, rarely actual abscesses, although frequently there is thrombosis and thrombophlebitis of the uterine and other pelvic vessels. If the infection be not extremely acute, or again as a result of long-continued congestion, a chronic metritis may result, with enlargement and diffuse fibrosis of the myometrium.

Perimetritis is but a form of localized peritonitis originating often in connection with inflammation of the adnexa or as an extension from acute metritis.

Tuberculosis.—Tuberculosis involves the body of the uterus, rarely the cervix and vagina; most often it is secondary to tuberculosis of the tube. Frequently the disturbance is not very characteristic; small-celled infiltration, not grouped into definite tubercles, may show here and there an occasional giant cell, but only upon special staining for bacilli is the nature of the condition surely recognized. Occasionally, however, large caseous tubercles are encountered, undergoing ulceration, and the process extends slowly but definitely into the myometrium.

Syphilis.—There has been much debate as to the extent to which the uterus is involved in syphilis. The primary sore may at times be detected either in the vagina or in the cervix or in its canal, but apparently infection may occur through the uterus without there being any recognizable primary sore. We refer particularly to those cases in which the child is born syphilitic, and the mother presents no primary or even secondary lesions, and yet the presence of the Wassermann reaction and the fact that the mother cannot be infected from the infant, as also the further fact that such a woman may give birth to a series of syphilitic infants, all indicate that she is infected.

Parasites.—Only rarely are **echinococcus cysts** found growing within the uterine wall.

Foreign Bodies.—As in the vagina, so here, foreign bodies may be found, necessarily less frequently. Attention must be called to the fact that portions of the placenta may remain attached, acting to all intents and purposes as foreign bodies, setting up irritation, and even tumor growth.

Regressive Tissue Changes.—Atrophy.—Just as the ovaries come to an end of their function at the climacteric, so the uterus, being functionally useless, undergoes shrinkage after the menopause. It becomes small, thin-walled, pale in color, and the cervical portion more particularly becomes diminished. In very elderly women, there is often to be found an accompanying congestion with hemorrhages of the fundal endometrium. This is not to be confounded with an acute infection.

Progressive Tissue Changes.—Hypertrophy.—Apart from the hypertrophy of pregnancy, there occur other hypertrophies, such as that arising from inflammation and from overwork; overwork hypertrophy, such as is seen when a large fibroid lies in the cavity, is likely to involve the muscle most, whereas that from inflammation need not do so. The formation of polyps, glandular hypertrophy, and even the formation of a decidua in extra-uterine pregnancy are all examples of localized hypertrophy.

Tumors.—These are of great variety and of much practical importance. The chief benign tumors are the **myoma** and **fibromyoma, lipoma, adenoma**, and so-called **adenomyoma**.

The most common tumor of the uterus is the **fibromyoma**, the so-called **fibroid**.

Study of the smallest and earliest of these affords examples of pure myomas, of a reddish color, vascular and moderately soft. Tumors of a larger size exhibit a combination of well-formed bands of unstriated muscle fibres alternating with bands of connective tissue, although careful examination indicates that much of this apparent connective tissue is formed of atrophied muscle fibres. The largest and oldest forms show great degeneration of the muscle, and are composed in the main of firm connective tissue. These are very dense and of a whitish color. In all forms, on section, the surface is glistening and has a watered silk appearance owing to the component bands being cut in various directions. These tumors are generally multiple and originate most often in the posterior wall, though with growth, they may come to be **subserous, intramural,** or **submucous.** Tumors of this order may even become detached from the uterus, and grow within the broad ligament, **intraligamentous.** Of these different forms, the intramural fibromas may attain the greatest size, becoming as large as an infant's head or larger. Subserous and submucous fibroids tend to become pedunculated, and with torsion of the pedicle the nutrition may be interfered with and as a result there may be infarction, necrosis, and gangrene.

These tumors are peculiarly liable to show various forms of circula-

tory and nutritive disturbances. Some are relatively vascular from passive congestion; others are œdematous, the lymph spaces becoming so much dilated as at times to give rise to a cystic appearance; at other times the general œdema mimics a **myxomatous** change (**myxomyoma**). Fatty degeneration is not uncommon, occurring in scattered areas, and beyond this, there may be indications of a localized or general necrosis, showing itself at times as a hyaline change or as a softening and autolysis with cyst formation, or not infrequently, as calcification, secondary to necrosis. A remarkable form of necrosis is that known as **acute red degeneration**, due apparently to sudden torsion of the tumor and obstruction of the blood supply. It appears to be a form of infarct. Rarely, apparently from metaplasia, nodes of actual bone or cartilage may develop within the tumors.

These degenerated fibroids may also become the seat of infection with resultant suppuration and gangrene, as a sequel of which submucous fibroids may undergo spontaneous evacuation.

The above myomas and fibromyomas are characterized by being well encapsulated and distinct from the uterine musculature in general. There is another form of tumor, however, in which the myomatous overgrowth is diffuse and not encapsulated, involving often a large area of the uterine wall and characterized by the inclusion of glandular acini, lined by columnar epithelium. It has now been proved absolutely by Cullen and others that these glands are extensions of the uterine mucosal glands deep into the modified myometrium. This has been confirmed by finding changes in these glands at the menstrual period identical with those seen in the uterine mucosa. These glands show no sign of active, independent growth; we deal not with adenomyomas but with a condition of **myomatosis with glandular inclusion**. The name adenomyoma, however, has taken such hold that it is difficult to replace it.

These myomas may undergo conversion into more malignant, sarcomatous growths. So, also, there are not a few cases on record in which the mucosa over a submucous fibroid has taken on carcinomatous growth, infiltrating the fibroid.

Adenoma and Carcinoma.—Polypoid overgrowth of the mucous membrane is not very uncommon; so also there may be such a localized overgrowth of abundant uterine glands that it is difficult to say whether we deal with an inflammatory or a neoplastic process. Nevertheless, at times, this adenomatous infiltration of the muscular wall may be so excessive that there can be no hesitation in speaking of this as a **malignant adenoma**, more particularly as secondary growths of adenomatous type may appear in the pelvic lymph nodes. This is one type of uterine carcinoma. Allied to this is the **adenocarcinoma** found in the cervical canal, and occasionally in the body. Here in place of typical there is atypical development of the glandular elements. This form appears to originate most frequently from the occluded glands and ovulæ Nabothi. This, like the former, infiltrates extensively the

muscle; with still more atypical growths, we obtain the pure carcinoma, with solid cell masses. Colloid cancer is distinctly rare.

This forms one group of uterine cancers; the other, and smaller group originate in connection with the squamous epithelium of the cervix, only a few cases having been recorded developing from the cervical canal or the body of the uterus. This, the **squamous carcinoma** or **epithelioma,** arises as a somewhat superficial growth, at times tending to be papillomatous, having a distinct tendency to ulceration and erosion with progressive invasion of the deeper tissues. It may extend thus, up the cervical canal into the body of the uterus, and slowly infiltrate the neighboring organs.

From the above description it will be seen that carcinoma involves all parts of the womb, but the cervix most frequently. Uterine cancer is one of the commonest of all forms of malignant growth and of carcinoma in the female, one out of every three cases is uterine. In the nulliparous, the condition is rare, and then most frequently affects the corpus, whereas in the woman who has borne children, the cervix is the part most often involved. This leads us to see some relationship between trauma and scarring of the cervix, and subsequent cancerous development. Cancer develops most often after the menopause, and we can but repeat the warning that a hemorrhage from the womb developing after the cessation of menstruation demands careful examination for the presence of a carcinoma.

Sarcoma.—Sarcoma is distinctly less frequent than carcinoma, is apt to arise at an earlier life period, and most frequently affects the body of the organ. The growths are pale, nodular, often multiple with extensive infiltration of surrounding tissues. **Endotheliomas** are still less common.

Cysts.—We have already referred to the ovula Nabothi and other retention cysts of the uterine glands, as well as to the necrotic and angiectatic cysts of uterine fibroids. **Teratomatous cysts** have been recorded.

THE FALLOPIAN TUBES

The Fallopian tubes may vary considerably in their position according to the relationship of uterus and ovaries. Their freedom of movement permits them to be included in any conglutination of pelvic surfaces and organs, and as a result they are distinctly apt to exhibit inflammatory and other disturbances. Again, their function as carriers between ovary and uterus permits them to become the site of gestation —**tubal gestation.** What is the cause of this is still a matter of debate. It is natural to imagine that slight bridges and inflammatory scarring of the mucosa of the tube by arresting the outward passage of the ovum favors its arrest in the course of the tube, but when we come to attribute the condition to gonorrheal or other salpingitis, the great frequency of the condition in some regions, as in certain parts of Western

Pennsylvania, is wholly out of proportion to the incidence of infection and the exact causation remains unexplained. Such ectopic gestation occurs, but with great rarity, in the ovary itself. Much more commonly it shows itself in the course of the tube, either toward the distal end, or in the central region or somewhat rarely in the uterine portion of the tube (**interstitial**). As a result, with the reaction on the part of the mucosa of the tube to form a decidua there is an extraordinary congestion of the blood vessels of the tube and as the gestation sac increases in size the walls of the tube become so much thinned that rupture may occur with escape of the fœtus into the peritoneal cavity or the broad ligament and associated profuse hemorrhage. In this new position the fœtus may gain a new placental attachment, and rare cases are on record, in which the foetus has developed to full term. Much more frequently

Fig. 364

Tubal gestation in the middle of the Fallopian tube. (Prof. Oskar Klotz.)

the uncontrolled hemorrhage leads to a fatal issue, or where the hemorrhage is not so extreme, the fœtus dies and becomes a lithopedion. These eventualities occur, of course, in the absence of surgical intervention. It is interesting to observe that a sympathetic decidual formation or change in the mucosa may show itself in the opposite tube or in the uterus.

Congenital Abnormalities.—The commonest congenital abnormality, so common as to be practically normal, is the presence of the **hydatid of Morgagni**, a cystic dilatation and enlargement of the longest of the fimbriæ. This is present in more than 20 per cent. of autopsies upon the female. Less commonly, variations are seen in the distal end. There may, for example, be a **double orifice** with a separate collection of fimbriæ around each, and very rarely the tube itself shows some duplication. **Diverticula** are sometimes noted. There may be complete **absence** of one or both tubes, generally associated with absence or malformation of the uterus.

Circulatory Disturbances.—These call for no special remark. In inflammatory states, there is acute **hyperemia**, at times with associated hemorrhage. The condition of **hematosalpinx** or accumulation of blood

in the tube is occasionally encountered by regurgitation of retained
menstrual blood, or, some hold, from actual hemorrhage in the tube
during menstruation.

Inflammation.—The more accurately the bacteriology of the inflamed
tube is studied, the more it is seen that gonorrhea is the commonest
cause of acute or subacute **salpingitis**. There may, it is true, be infec-
tion by the strepto- and staphylococcus, but these are not so frequent.
The results are a swelling of the mucosa with pronounced purulent
secretion which in cases of obstruction of the tube pass on to its great
distension with actual pus (**pyosalpinx**). A marked characteristic
of gonorrheal salpingitis is that while the lumen of the tube may be
filled with ordinary pus cells, coincidently the greatly infiltrated sub-
mucosa may show an extreme accumulation of plasma cells. Recent
authorities hold that this abundance of plasma cells is pathognomonic
of gonorrheal infection. With this infiltration of the submucosa,
the mucous membrane shows pronounced loss of epithelium and the
rugæ are flattened, so that the mucosa becomes less infolded. This
very destruction of the mucosa favors the subsequent formation of
bridges and bands of connective tissue with stenosis. It is characteristic
of this acute inflammation of the tube, that the ends are apt to become
sealed; and even while at first this sealing be through swelling of the
mucosa and the viscid nature of the secretion, it is apt to be ultimately
followed by organized obliteration, with consequent sterility. A
second point is that with this sealing and subsequent distension of the
tube, the fimbriæ are apt to become inverted with complete disappear-
ance; a third, that despite the great distension, the tube adapts itself
and rupture rarely occurs.

According to the grade of inflammation, we obtain conditions. of
hydrosalpinx and **pyosalpinx.** Pyosalpinx is the result of a continued
suppurative infection. Hydrosalpinx occurs where there has been a
previous inflammation that has sealed up the tube and then came to an
end, and is the expression of the continued secretion from the mucosa
of its normal product, a mucoid fluid.

As with the appendix, so here, inflammation involving primarily the
mucosa is liable to spread through the walls and induce a perisalpingitis,
which in acute cases may be suppurative, leading to an acute pelvic
peritonitis. More frequently this assumes the form of an adhesive
inflammation with extensive adhesions so that the tubes and all the
pelvic contents are densely bound together.

Specific Infections.—Next in frequency to gonorrheal is tuberculous
salpingitis. While this may be of hematogenic origin, it appears fre-
quently to be induced by bacilli carried down the tube in the peritoneal
fluid, from the ovaries or other abdominal organs, or upward from the
uterus and vagina. In the early stages the changes are not characteristic;
there is a small-celled infiltration of the mucosa and submucosa with
generalized thickening of the tube. Later, tubercles with caseous
centres are to be made out, and the whole interior of the tube may show

extensive fused tubercles with advanced caseation, which with stenosis of the ends of the tube may lead to a condition simulating pyosalpinx, the greatly distended tube filled with soft, cheesy, or thick puriform matter (**tuberculous pyosalpinx**). Here again the tuberculosis process is liable to extend outward involving the serosa and leading to tubercle formation with adhesions.

Syphilis.—Contrary to expectation syphilitic lesions in the Fallopian tubes are distinctly rare. Gummas have been recorded. So also there are a few cases of actinomycotic lesions, due to a secondary and descending infection.

Progressive Changes.—Productive inflammation may show itself as a distinct overgrowth of the mucosal folds, and with the abundant infolding of the mucosa the enlarged tube may on section be mistaken for an adenomatous development composed of abundant branching glandular acini lined by columnar epithelium. Primary tumors are infrequent; **papillomas** and **carcinomas** are encountered, and a few cases of **myoma, fibroma,** and **lipoma** are on record.

THE OVARIES

The average adult ovary may be said to be somewhat of the size and shape of the first phalanx of the adult male thumb. The ovary is developed from the Wolffian body by the ingrowth of the germinal epithelium. It is from these ingrowths that the Graafian follicles, with their contained ova, are developed. The stroma, on the other hand, is of connective-tissue origin. The ovary is thus entirely mesoblastic, and tumors arising from it, even if histologically of carcinomatous type, are mesothelial (mesotheliomas), or mesenchymatous.

When the follicle ruptures and the corpus luteum takes its place, lutein cells arise which apparently have a specific function of temporarily preventing ovulation by causing degeneration of nearly ripe follicles and retarding the maturation of others. If the corpus luteum be removed, ovulation proceeds at once. Presumably the secretion has an effect in anchoring the embryo and maintaining its fixity in the early stages of pregnancy, the uterine mucosa becomes sensitized so that it will form the material part of the placenta in response to the stimulus supplied by the fertilized ovum. Further, the internal secretion of the corpus luteum stimulates growth of the mammary glands.

Abnormalities.—One or both ovaries may be wanting, and this usually accompanies other grave defects of the genito-urinary system. There may likewise be **hypoplasia** of one or both, with a relative absence of Graafian follicles. So also occasionally **accessory** ovaries have been encountered. Of abnormalities of position the most important congenital condition is descent of the ovary into the canal of Nuck, simulating the descent of the testis into the inguinal canal.

Circulatory Disturbances.—It is notable that active hyperemia of the ovary may be extreme in the menstrual period, leading to such dilata-

tion of the arteries that, as in the uterus after pregnancy, there may be a subsequent reduction in size of the vessels by means of new growth of the intimal tissues. The vessels similarly may show passive hyperemia in obstructive cardiac disease or from torsion or other local obstruction to the venous outflow. Physiological hemorrhage occurs into the site of the ruptured follicle—the **corpus luteum**—and pathological hemorrhage, generally localized, is found in various acute infections.

Inflammation.—Oöphoritis.—In all cases of acute peritonitis the ovary is found reddened and congested: it may even be infected in general bacteriemia; but by far the most frequent causes of inflammation lie in the spread of infection from connected structures, especially the tube, and this notably from gonorrhœal virus. The inflammation so set up may be diffuse or follicular, and as a result, the ovary may be soft, enlarged, and œdematous, or suppuration in small or large areas be seen. The entire organ may be converted into a sac of pus, which may rupture: such a change is usually accompanied by fixation to the tube and other nearby structures, so that a mass of inflammatory material is found in which it is recognized that both ovary and tube have participated. This is known clinically as a **tubo-ovarian abscess**, and may arise equally from either constituent.

A frequent result of oöphoritis is that pelvic adhesions result, and the inflamed ovary is often found in Douglas's pouch. In considering the genesis of ovarian abscesses, it must not be forgotten that the very frequently seen follicular cysts of the ovary may become infected.

Chronic Oöphoritis.—In this the ovaries are found dense, of an ivory color, and while they may be smooth, the surface is usually corrugated, with or without adhesions. Warning must be given that a similar external appearance is seen in the shrunken, atrophic ovaries of old women. In the younger adult, this thickened condition of the outer layer of the ovary is due to an inflammatory fibrosis, and is important in that, obviously, it hinders the rupture of the follicle and the escape of the ovum. Such unruptured follicles undergo degeneration and become converted into small cysts, which are a characteristic feature in ovaries of this order. The stroma in general shows an increased fibrous hyperplasia. Chronic inflammation of the ovary usually results from continuance of an acute infection or from recurrent attacks of a mild irritant. **Tuberculosis** and **syphilis** are rare in the ovary.

Regressive Tissue Changes.—We have already referred to the **atrophic** and fibrotic condition secondary to oöphoritis. It was there stated that a somewhat similar appearance is encountered after the menopause. As a result of menstruation **hyaline** and **elastoid** changes are seen in the arteries.

Progressive Tissue Changes.—Tumors.—If a morphological classification be used, it is likely to be incorrect embryologically, for the etiology of many of the ovarian growths is yet in doubt.

It is possible to divide them roughly into the cystic, the cystic and solid mesotheliomatous or carcinomatous tumors, the connective-tissue

growths and the teratomas, a division which will serve to prevent confusion.

Cysts.—These are of great variety, and it may be stated by way of preface that they can originate from the follicles, from the germinal epithelium, or from Wolffian "rests."

1. *Cystic Degeneration of the Ovary.*—This is characterized by the appearance of numerous small cysts throughout its substance, lined by a single layer of cells, in places ciliated; there is no follicular epithelium of the usual type, and no ovum. They may be found in the newborn. The wall is constituted by the thickened wall of the follicle, and the fluid is clear. It seems likely that an ill-timed ripening of a follicle is responsible for their occurrence.

2. *Follicular Cysts.*—These are of the nature of true retention cysts. Usually these cysts are multiple and small, but occasionally a single larger cyst is found. When small they are lined by cylindrical epithelium and at times a persistent ovum is seen. When large the epithelium, through pressure, is flattened; they contain a limpid fluid. Quite analogous to these are the cysts originating in corpora lutea, usually to be known by their thick, wavy, hyaline wall. In these the fluid is apt to be colored by modified blood pigment.

FIG. 365

Section through ovary exhibiting multiple follicular cysts of varying size (*a, b, c, e,* and *f*); *d,* Fallopian tube. (McGill Path. Mus.)

3. *Cystadenomas* (*Cystomas,* or *Glandular Pseudomucinous, Multilocular Cysts*). The alternative names, taken together, describe fairly accurately these cysts, the most common neoplasm that is found in the ovary. They are unilateral or often bilateral. Now-a-days they are usually removed by operation before reaching a great size, but formerly cases have been described in which the weight of the cyst exceeded that of the patient after its removal. The mass consists of one main cyst of large size, with several subsidiary or daughter cysts, which may exist independently in the stroma or may encroach upon the cavity of the major cyst. On the inner wall are ridges representing former divisions between the cysts, the larger cyst being developed from the confluence of smaller ones. The cyst wall is tough, thin, and translucent, but in some cases thick, its blood supply being the large vessels that ramify on the surface. The fluid is of varying consistence, thinnest in the largest cyst, having a specific gravity between 1010 and 1030. It may be viscid, mucinous, clear, glassy, turbid, brownish, or at times bloody. Bodies related closely to mucin (pseudomucin) and albumin are present in the fluid.

The cyst wall is composed of two layers, the outer dense and fibrous, the inner cellular and vascular. A single layer of cylindrical, columnar cells with basally placed nuclei lines it internally (see Fig. 215, p. 410). This epithelium has a pronounced tendency to form multiple papillary ingrowths, and an equal tendency to give origin to downgrowths into the cyst wall, which, becoming snared off, develop into secondary cysts. Microscopically, the lining cells are distinctly mucinous, but they may show various kinds and grades of degeneration. In addition to pseudo-mucin the fluid may contain fat globules, leukocytes, degenerating cells, blood, and cholesterin. The position of the cyst in relation to the tube is characteristic. The tube can be lifted off the cyst, except in those rare cases in which the cyst develops between the layers of the broad ligament.

Fig. 366
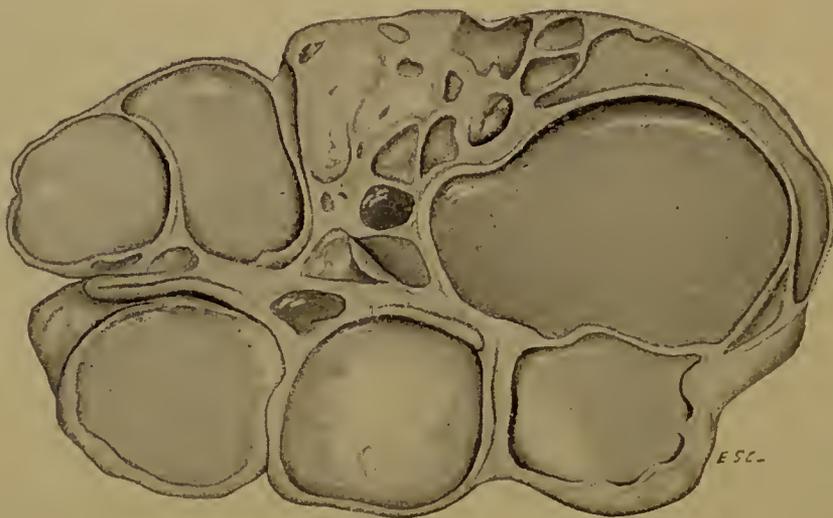
Multilocular ovarian cyst.

With the continued growth of the cyst, it lifts itself out of the true pelvis and elongates the ovarian ligament, which, acting as a long pedicle to a relatively movable growth, is liable to be twisted, shutting off the circulation. The cyst wall then becomes dark red in color, and its tissues may show all grades of hemorrhagic infarction, even to necrosis. A large cyst may break and discharge its contents into the peritoneum, where the mass of mucinous material may be walled around, and form a kind of false mucinous tumor (**pseudomyxoma peritonei**).

Papillary Cystoma (Cystadenoma Papilliferum).—A well-known clinical variety of this order of tumor is the so-called cystadenoma papilliferum, in which the papillary growth is very pronounced. The cavity or cavities are more or less filled with warty, villous or tree-like excrescences formed of proliferated stroma covered by ciliated cylindrical epithelium. The stroma is fairly vascular, but may undergo a mucinous degeneration. When the papillæ appear, as they sometimes do, on the outside of the cyst, it means that a rupture of the cyst wall has occurred, permitting the papillæ inside to burst forth; sometimes the papillæ actually invade the cyst wall. In such a case the cystic quality of

the tumor has receded and it approximates more than before to a papilloma.

The fluid is thin and watery, at times bloody in appearance. The tumor is an important one, because in time it becomes malignant (a quality foreshadowed by its infiltrating its own wall), giving rise to secondary nodules on the peritoneum. The origin of cystadenomas has led to much discussion, and the question is still an open one. Leaving this question necessarily unsettled, there is a natural transition to the carcinomas, considering the great liability for the benign tumors, especially the cystic ones, to become malignant. Like the cystadenoma, carcinoma of the ovary has been found in early life, even before puberty.

Carcinoma.—These are **cystic** and **solid**, the former arising in the simple cystadenomas, or even more frequently, in the papillomatous ones. In the former, which in general resemble their non-malignant prototypes, the walls and septa are infiltrated with nodules which are masses of epithelial cells. Multiple rows of cells replace single rows; the fluid contents are cloudy from admixture of cells and blood, at times viscid, or even colloid.

In the papillary type (**cystadenoma papilliferum malignum**), the frankly malignant form of the type above described, the papillæ grow exuberantly, and the septa are infiltrated with papillomatous masses, which may grow right through the walls and appear externally, giving rise to peritoneal and broad ligament metastases, and to secondary growths in distant organs. At times it may be difficult to determine whether a given carcinoma is primary in the stomach or the ovary.

The solid carcinomas of the ovary form smooth or nodular growths of large size and may be unilateral or bilateral. They may be of uniform, rather soft consistence, and exude a milky fluid on pressure, or may be scirrhous or even colloid. Histologically, they may be diffuse, alveolar or may simulate tubules of cylindrical, cuboidal, or polymorphous cells. An abundant deposit of calcareous material may give rise to **psammocarcinoma.**

Ribbert regards these as embryomas in which the entoderm or hypoblast alone has undergone development, and compares the papillary growth to chorionic villi. We are not prepared to accept this view, but, from the studies of our colleague Dr. Goodall, are inclined to believe that the origin is from certain remarkable downgrowths of the germinal epithelium which do not undergo development into Graafian follicles, but are found persisting in about 10 per cent. of human ovaries, in the form of spaces or cavities, lined by an epithelium which, according to life period and stage of development, is curiously variable in its characters. An interesting feature about these persistent growths is that they show a marked liability to the formation of capillary ingrowths, as again to the development of outgrowths at times solid, at times glandular or cystic, into the surrounding ovarian tissue. We possess here, in short, an organ or part capable of giving origin to multiple cysts and to intracystic ingrowths.

Connective-tissue Tumors.—Of the connective-tissue tumors, the most important are **fibroma, adenofibroma, cystofibroma, myofibroma, endothelioma, perithelioma,** and **sarcoma.** Fibromas usually form diffuse overgrowths with uniform enlargement of the ovary, but may be circumscribed nodules, unilateral or bilateral.

The **sarcomas** are not nearly so common as are carcinomas of the ovary. Like so many of the ovarian tumors, they tend to be bilateral: they may be round-celled, spindle-celled, or giant-celled, and it has been suggested that the last originate possibly from the interstitial cells which are of like origin with the cells of the Graafian follicles. Some cases are on record of true **carcinoma sarcomatodes.** These perhaps represent transitional types seen in tumors of mesothelial origin.

Endotheliomas are occasionally encountered, but, here again, there is a great liability to classify complicated and doubtful tumors of the transitional type as either endo- or perithelioma. Much fuller study is necessary before we can properly classify the ovarian new growths.

Teratomas.—These constitute a class apart and are not uncommon. They are embryomas, or as stated on p. 324, the result of aberrant growth of totipotent ovarian germ cells. They are generally cystic, although solid forms consisting of cells derived from all three germ layers are at times met.

Cystic Teratomas.—Appearing as cysts of any size up to five or six inches in diameter, usually solitary, but sometimes multiple and bilateral, these are specially prone to appear after puberty. On opening, the cysts are seen to contain tallow-like contents, mixed with hair; sometimes the contents are thin fluid with tallowy masses. The hairs are fixed to skin resembling the scalp, which covers a knobbed part of the inner surface, the rest being covered by what looks like mucous membrane. Underlying the knob may be bone, and in it are often incisor teeth, sometimes in a row as in the jaw. Microscopic examination through the knobbed portion shows hair follicles, sebaceous and sweat glands, portions of bone and cartilage, sometimes structures of the eye; in fact, almost any structure found in the embryo may be seen, and even attempts at limbs have been observed.

Solid Teratomas.—The solid teratomas are less common. The tumor on section shows multiple small cysts with serous, mucinous, or tallow-like contents, lined by ciliated, columnar or 'flat epithelium, in its solid parts muscle, cartilage, glial tissue, and so on; but as a general rule, the solid teratomas contain less developed tissues than the cystic, and are more prone to malignant development with secondaries in other organs. Cystic teratomas, it is true, frequently undergo a carcinomatous development, the tumor growth being of various kinds, even chorio-epitheliomatous, and the metastases may be also of mixed nature, although sometimes of only one kind of malignant tissue. Before leaving the "mixed tumors" of the ovary, it may be pointed out that there are two kinds, those in which different tissues develop independently and simultaneously (mixed tumors proper), and those in

which a secondary transformation occurs in the previously existing neoplasm (**tumor in tumore**). Almost every known combination of benign and malignant growths has been observed.

Teratomas are liable to complications of various sorts; twisting of the pedicle may lead to anemia, hemorrhage, or necrosis; inflammation may result in adhesions or suppuration with rupture into surrounding organs, the peritoneum or to the outside. If the more serious results do not ensue, there is at least congestion, œdema, and the formation of degeneration cysts; hyaline or calcareous degeneration, also, may occur.

RELATED PELVIC STRUCTURES—THE LIGAMENTS, THE PERIMETRIUM, THE PARAMETRIUM, AND THE PELVIC CONNECTIVE TISSUE

Congenital Anomalies.—Various modifications of the ligaments can occur, governed by the **absence** or **anomalous position** of the more important organs with which they are connected; remains of the parovarium and the paroöphoron may give rise to **cysts.**

Circulatory Disturbances.—The veins in all these structures may be dilated, tortuous, thrombosed, or (especially those of the ovarian or pampiniform plexus) the seat of **phlebolith** formation. **Hemorrhage** may arise from many different causes connected with the pelvic organs, and the course of the blood varies, according to whether it is intra- or extraperitoneal. If into the peritoneum, it may gravitate into Douglas' pouch and form a **postuterine hematoma** or **hematocele**; if in large enough quantity or circumscribed, it may enlarge the space between the uterus and bladder, as an **ante-uterine hematoma.** If extraperitoneal, it may infiltrate diffusely all the loose connective tissue of the pelvis, or may be between the layers of the broad ligament (**intraligamentous hematoma**). In any case the blood may be **absorbed** and leave traces as pigment; or being partly unabsorbed may undergo **organization** and be walled off, the occurrence being marked finally by the presence of a mass of fibrous adhesions; or while still fluid it may **rupture** the wall of some organ and escape; or being infected, may become the basis of an **abscess.** The hemorrhage of greatest importance is that due to a ruptured ectopic gestation sac, although bleeding may also occur from rupture of a Graafian follicle, from a cyst, from the escape of blood from the abdominal end of the tube, or accidentally after an operation.

Inflammation.—According to situation, this may be **parametritis**— that is, cellulitis of the pelvic tissues, or **perimetritis**, a localized peritonitis affecting the uterine serosa.

Parametritis.—Infection of the pelvic connective tissue arises from extension of a gonorrhœal or other infection of the passage, or from injuries in parturition or from puerperal sepsis. The exudate may be serous, or the tissues diffusely infiltrated with pus, or there may be

localized abscess formation, and even gangrene. Where pus is formed it may burrow to the abdominal wall, the thigh, the floor of the pelvis, or may perforate into some of the viscera. If healing of such a state occur, it will be at the cost of much adhesion and fibrosis. The soggy, inflamed tissues of a parametritis are clinically known by that good descriptive phrase, "**the (inflammatory) pelvic mass.**" Whatever area is affected, Douglas' pouch is sure to suffer, sooner or later, by reason of its position, and abscess in this area is frequent (**retro-uterine abscess**). In all these inflammations, the adhesions are an important factor; in a low grade of infection they may be the chief abnormal fact (**productive pelvic peritonitis**), and may lead to all sorts of distortion and occlusion; in an ordinary case, their position may determine the localization and ultimate course of the fluid exudate.

Progressive Tissue Changes.—The round ligaments may **hypertrophy** along with the uterus, and the broad ligaments with ovarian or parovarian cysts.

Tumors.—The tumors found in the broad ligament are in the main derived from the uterus, where they are not of ovarian origin. The growths are mostly benign, **myomas, fibromas, lipomas,** and even **adeno-myomas** of the type already described as originating in the uterine wall.

Cysts.—Mention should here be made of **parovarian cysts,** which arise from the parovarium. A parovarian cyst may grow as large as a man's head. It lies at first between the abdominal end of the tube and the ovary, and as it develops the tube and ovary may be widely separated and greatly flattened. There is generally no pedicle, and the wall is thin; internally the wall may show papillate ingrowths. The contained fluid is watery, and has a low specific gravity.

Teratomas ("dermoid cysts") have been found in the pelvic connective tissues, and **sarcomas** can arise from these tissues; carcinoma is always secondary.

THE PUERPERAL UTERUS

Apart from hemorrhages connected with the injuries of labor, and with imperfect involution, and hemorrhage due to accidental disturbance of the placenta, diseases of the puerperal uterus centre around infection. As a result, endometritis, metritis, or "puerperal fever" may supervene.

The offending organisms are most often the streptococcus pyogenes and the staphylococcus, and the predisposing causes are lack of cleanliness and meddling, usually in the way of examination, douches, and improperly undertaken instrumentation of the lining of the uterus. The infection may be membranous: in general, the placental site is most affected, the surface being gray or brown or even green in color.

In addition to this, there may be infection and decomposition of retained foetal products, blood, or lochia. The uterus of such a case is enlarged, the wall œdematous, the endometrium dirty green or

brownish-black in color, stinking and pulpy, the wall of the uterus soft and rotten. Microscopically, in either case, the tissues stain badly and areas of necrosis or of infiltration are seen according to the varying severity of the infection. Bacteria can usually be readily demonstrated on the surface and in the tissues.

In slight cases of puerperal infection, there is no such serious state; the placental site, it is true, is ragged and unclean looking, but if drainage be efficient the affection subsides with no further consequences. For practical purposes, it must be remembered that an intra-uterine douche at such a time often serves to produce an alarming state of fever and rapid pulse, due to the sudden release and absorption of toxins; it is always to be remembered that treatment, to be efficient, *must inflict no further lesion on the uterine wall.* Another extremely important fact to be kept in mind is that despite the statements of anxious practitioners to the contrary *fever in the puerperium is most likely to be due to infection of the genital tract.*

In the pregnant uterus, if the patient is suffering from infectious disease, endometritis may arise from hematogenic sources; if of low grade, the decidua may be merely thickened, but if severe, purulent secretion is found, which instead of being discharged, may be retained between the deciduæ; hemorrhage and abortion are likely to ensue.

Metritis.—It will be evident that any severe case of puerperal endometritis is accompanied by a corresponding metritis, which need scarcely be considered by itself, further than to point out that the metrium may be the seat of a diffuse serous or purulent infiltration or of multiple abscesses; on the other hand, the metritis may consist of little more than an infection of the lymphatics or of the vessels with thrombosis. From such beginnings the lymphangitis may spread to the diaphragm, the thrombophlebitis to the vena cava, the infection to the peri- and parametrium, and an extensive pelvic cellulitis and peritonitis be the result; frequently, and most serious of all, a bacteriemia arises (*puerperal septicemia*).

Progressive Tissue Changes.—**Tumors.**—The tumor specially connected with pregnancy is the **chorio-epithelioma malignum**, otherwise called **deciduoma malignum, syncytioma, syncytial carcinoma,** and many other names. It has been elsewhere explained (see p. 330) that this is to be classed as a teratogenous blastoma. When it appears in the uterus it is an evidence of previous conception, although this may have occurred long before.

This tumor tends to form polypoid or fungating growths projecting into the uterine cavity, but quickly invades the endometrium and the uterine vessels. It is of reddish color, often hemorrhagic, and soft, friable, and spongy.

The growth originates by proliferation of Langhans' layer of the chorionic villi; these cells, instead of undergoing syncytial change, remain active and proliferative. After they have proliferated in abnormal situations, they may, it is true, undergo the usual transforma-

tion into syncytium. The deeply infiltrating parts may show an alveolar structure, but the spaces possess no special lining and the tumor has no stroma and no blood vessels. The syncytial elements when present are in the form of plasmodial giant cells. The cells of the Langhans' layer tend to be spherical, and are grouped into masses of varying size. In the secondaries, they possess all their original power of erosion.

Mention has been made of the readiness with which this tumor metastasizes; the vagina is very often an early seat of extension.

THE PRODUCTS OF CONCEPTION

The Placenta

The pathology of the placenta is not very well understood, and few of its morbid states are recognizable at first glance. Its size and its place are variable; its size, if extreme, is often in keeping with that of the child; usually single, there have been seven reported with one fœtus; accessory placentas of small size (**placentæ succenturiatæ**) are often seen. The position of the placenta would be a matter of little moment were it not for the fact that its displacement causes it to interfere with the opening of the uterus, and it is torn and bleeds at parturition—**placenta previa**. It is considered that endometritis is a predisposing factor in the occurrence of placenta previa.

Circulatory Disturbances.—Among vascular changes, it may be said that pressure upon the cord by knotting, torsion or other means may make the placenta **anemic** or, more probably, **hyperemic**, the veins being more compressed than the more resistant arteries. **Thrombosis** may result in **placental infarct**, a brown or yellow area with altered blood clot that ultimately may undergo organization. **Hemorrhage** is the most important of these circulatory changes, because effused blood may separate the placenta from the uterine wall, and so cause abortion. **Œdema** of the placenta occurs as the result of extreme congestion, and in hydramnios and cases of general anasarca.

Inflammation.—Tuberculosis.—Occasionally in a woman the subject of widespread tuberculosis the placenta may be infected from the blood, and the rare event happens of a child born with tuberculosis; such tuberculosis is congenital, not hereditary.

Syphilis.—Syphilis leads to cellular infiltration of the placenta; the arteries may also be the seat of syphilitic endarteritis.

Regressive Tissue Changes.—**Hyaline** and **fatty degeneration**, and **necrosis**, followed at times by **calcification** are all known as results of circulatory disturbances.

Progressive Tissue Changes.—We have already (p. 328) called attention to the results of retention of the placenta in the production of different forms of placental mole—**fleshy mole, hydatidiform mole,** and the **chorio-epithelioma malignum**. For the placental tissue to take on

other forms of new growth is singularly rare; nevertheless, **fibroma** and **fibromyoma** have been described. The **angioma**, also recorded, is presumably a condition of **hemangiectasis**. As regards **cysts**, these may be either necrotic, secondary to localized infarct, or occasionally in an otherwise normal placenta, the villi of a restricted area may show œdema and the production of a condition simulating the hydatidiform mole.

FIG. 367

The Umbilical Cord

The cord varies greatly in length, both extremes being troublesome at parturition; if the omphalo-meseraic duct does not properly close, the intestines may protrude into it (**hernia of the cord**). The chief interest in diseases or pathological change seen in the cord attaches to the bearing which these have on parturition or the state of the fœtus. Thus it may be **twisted** or **looped** about the fœtus or some part of it, so as to cause even amputation of a limb in early fœtal life, or strangulation at birth. Sometimes deep grooves are made upon the body surface by pressure of the cord.

Various **degenerations** of the usual kinds may be wrought in the cord by disturbance of its circulation, and **septic infection** of the cut end may lead to infection of the infant by way of the arteries and veins, which become inflamed.

Syphilis of the cord is seen as a smallcelled infiltration around the vessels; **myxoma**, **angioma**, and **cysts** are occasionally found.

The Amnion and the Amniotic Fluid

The amnion may **press** upon the fœtus, so that development of a part or parts may be hindered; actual adhesions may occur. If the outflow of blood and lymph be obstructed, **giantism** of a part may ensue.

Girl, aged ten years, showing cicatricial grooves due to constriction of umbilical cord. At birth, according to the mother, the grooves in the abdominal wall and left thigh were occupied by the cord. (Hawthorne.)

The amniotic fluid may be excessive in amount (**hydramnios, polyhydramnios**) or it may be diminished (**oligohydramnios**). It may be contaminated by fœtal excretions so as to be dirty and foul, and may undergo infection and putrefaction.

The Fœtus

The **death** of the fœtus may be followed by its expulsion, but if not expelled, it may macerate and disintegrate, coming away gradually in pieces; or a drying-up process (**mummification**) may ensue, or even calcification (**lithopedion**). Death of the fœtus *in utero* is often due to syphilis, and various forms of acute or chronic disease in the mother, producing toxemia, may suffice to kill it.

Ectopic gestation may take place in any part of the tube, but is most common at the entrance of the tube to the uterus (**interstitial gestation**) and in the mid part of the tube. It is not likely that abdominal gestation ever occurs, the fœtus that is found in the abdomen having been extruded from the tube (**tubal abortion**). To this we have already referred on p. 753.

Fig. 368
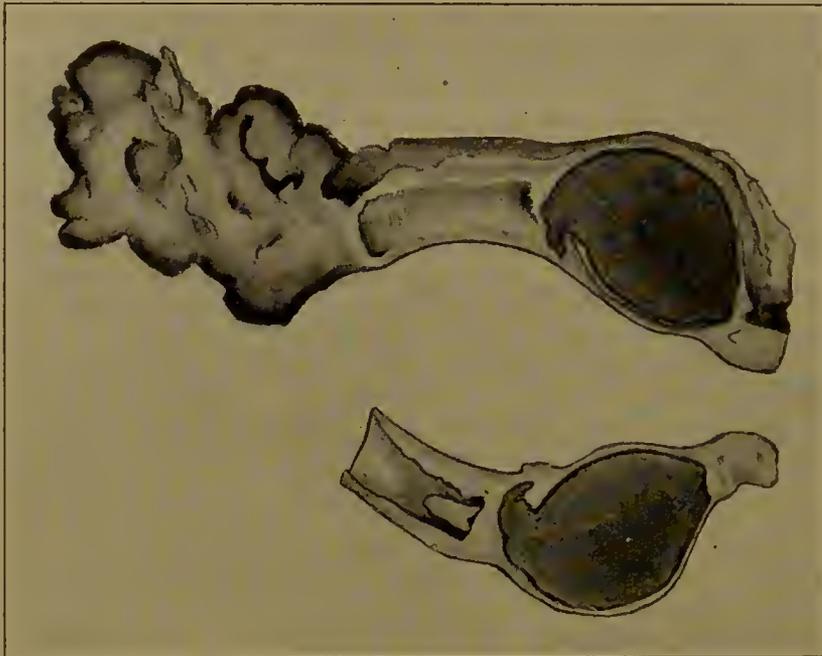
Tubal gestation, cut in section, showing the blood clot, situated close to the uterine end of the tube. (Prof. Oskar Klotz.)

The chief danger in ectopic gestation lies in the liability to severe hemorrhage at the time of rupture, and the necessity for operative delivery, for as will be easily imagined, there are but few cases that admit of expulsion by the natural channels. The causes of ectopic gestation are inflammatory, such as the existence of gonorrhœa, or some obstruction, either by bending or folding of the tube or by the presence of a tumor or other obstacle to the passage of the ovum.

THE MAMMARY GLAND

The diseases of the breast belong alike to both sexes, but by reason of its function in lactation, the female breast becomes of prime importance; in the male, a consideration of its diseases would be a very simple and brief matter. The mammary gland is branched, and at the onset of pregnancy the single lobes become compound and many new acini are formed, while the vascularization and stroma advance equally in their development; at the time of delivery, the first expression brings from the gland **colostrum**, in which the "colostrum corpuscles" are cells that have wandered into the acini and have engorged themselves with the fat corpuscles that lie therein; after their dislodgement, the globules are, in the regular way, the product of the mammary cells. When the function of lactation is finished, the breast, as a whole, becomes smaller and once more simplified.

Congenital Anomalies.—**Amazia** or **amastia**, absence of the breast, often bilateral, is generally associated with lack of ovarian development, and **hypoplasia**, the infantile breast, accompanies an infantile state of the sexual organs in general. **Microthelia**, an abnormal smallness of the nipple, may lead to difficulty in suckling. Abnormal development of the breast in the male (**gynecomastia**), reduplication of the nipple (**polythelia**) or of the breast itself (**polymastia**) are observed. **Accessory breasts** may be seen in such a situation as the axillæ, from pinched off lobules (**aberrant mammæ**), and such, as well as the ordinary supernumerary breasts, can produce milk.

Circulatory Disturbances.—Swelling of the breast sometimes characterizes the premenstrual period, and occasionally **vicarious menstruation** is exhibited by discharge of blood from the nipple. **Hemorrhage** and the formation of **hemorrhagic cysts** may result from trauma either primarily or by bleeding into a preëxistent cyst.

Inflammation.—Inflammation may arise in the breast at any period of life, even in infancy, but it is most often found during lactation, where infection gains entrance through the nipple canal, or more frequently by way of small fissures or cracks in the nipple. Rarely the breast suffers by extension of inflammation, as where the infection from a carious rib or a ruptured empyema reaches its tissues. **Thelitis,** inflammation of the nipple, and **areolitis,** of the areola, occur, with the formation of abscess, the so-called **antemammary abscess.** Inflammation of the breast tissue itself (**mastitis**) is the most common form; the breast is enlarged, tender, and sometimes reddened; it may be possible to press pus from the nipple (**galactophoritis purulenta**), or there may merely be evidence of a deep abscess or of several such; more rarely, the entire breast is in a state of purulent infiltration (**mastitis phlegmonosa**). However the infection may have reached the breast, the interstitial tissue is seen microscopically to be infiltrated, while the glands contain a semipurulent material in which are abundant desquamated

degenerated gland cells and leukocytes. If the disease be not relieved, the abscesses may coalesce, and the entire breast be riddled, and the pus may travel far for an outlet, may break through the skin or even into the thorax. An opening into the skin may establish a fistula through which milk, mixed with inflammatory products, may escape. A non-suppurative mastitis may quickly resolve; abscesses if evacuated may heal with scarring, and it not evacuated, the pus may inspissate, and calcareous deposit occur; in a much scarred breast, the onset of a new pregnancy may be attended by the development of retention cysts. The so-called **retention mastitis** is nothing more than infection of a breast in which there is already an irritation caused by the presence of stagnant gland secretion.

Fig. 369
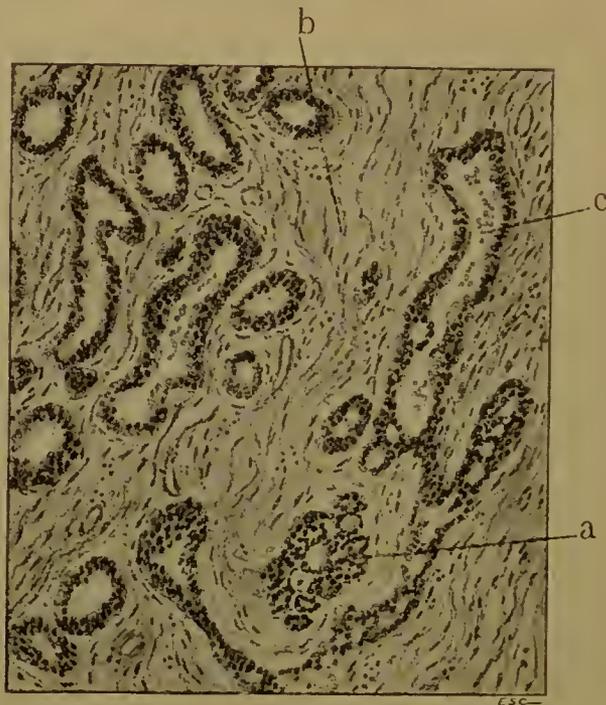
Fibro-adenoma of breast affording indications of overgrowth and aberrant growth of the glandular elements: *a*, compressed acini; *b*, fibrous overgrowth; *c*, a somewhat dilated duct, with epithelial proliferation.

Tuberculosis.—Tuberculosis occurs with fair frequency in the breast, occasionally as **diffuse miliary** tuberculosis, but oftener as **caseous areas**, and as **cavities**, from which fistulæ may open. The edges of the fistula are covered by granulation tissue and the discharge is thin pus. The axillary lymph nodes also show caseation, and may even break down and discharge. In the case of both these forms of tuberculosis the infection is hematogenic. **Syphilis** may occur on the nipple as the primary lesion, and diffuse and gummatous infiltrations may arise in the breast in the later stages, while the skin of the breast may exhibit specific changes, as the skin elsewhere.

Regressive Tissue Changes.—**Atrophy** of the mammary gland occurs at the menopause and sometimes after removal of the ovaries, although the loss may be compensated or overcompensated in bulk by fat, without which the breast becomes small and flabby. Microscopically,

thickening and hyaline degeneration of the walls of the ducts occur, so that they appear as yellowish-white lines in the tissue.

FIG. 370

Pericanalicular fibroma of the mammary gland. The glandular acini and ducts are prominent and show some irregular overgrowths of the epithelium, but the main feature is the development of connective tissue both periacinous and interstitial, the latter not sharply defined. (Ribbert.)

FIG. 371
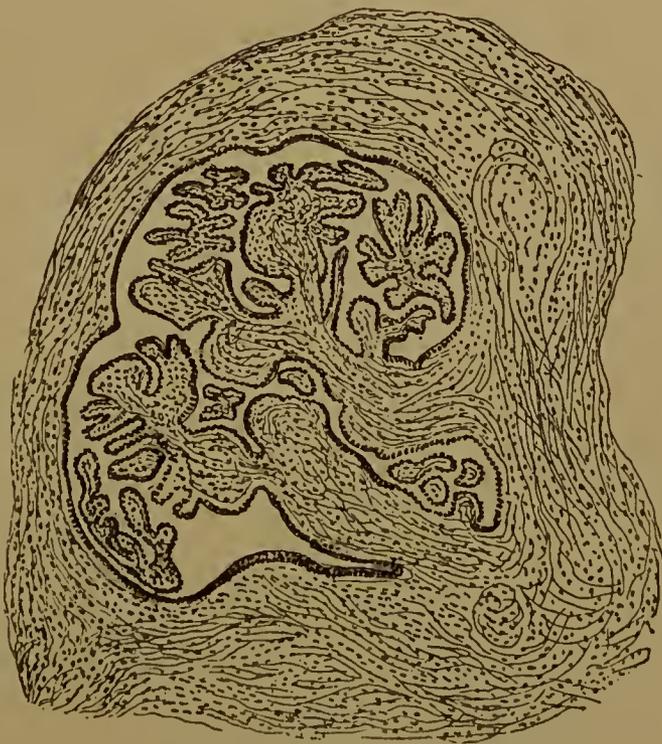
Intracanalicular fibroma or intracystic papilloma of breast. (Orth.)

Progressive Tissue Changes.—Regeneration of destroyed tissue occurs only to a slight extent; compensatory hypertrophy of the rest of the gland is a more frequent happening, and is not confined to preg-

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nancy but may happen in cases of new growth of the uterus and ovaries. Rare cases are observed, usually in the young, of a kind of neoplastic overgrowth (**giantism of the breast**) in which a breast has attained a weight of sixty-four pounds. There is also diffuse overgrowth that sometimes is of the nature of **fibromatosis**, at others of **adenomatosis**, or of both together. The nipple does not share in the general enlargement.

Tumors.—These are of considerable complexity and of great practical importance because of the preponderance of malignant forms of growth; because they are readily accessible to surgical removal, the pathologist's opinion is frequently asked, and the decision is often very difficult to make. Because of the liability to error, and the frequency of malignant tumors in this site, it has become a surgical rule to advise the removal of any growth whose nature is at all doubtful. Although the male breast is able to show examples of all the tumors to which the female breast is liable, it does so relatively infrequently; the latter is in a state of physiological and anatomical instability throughout the years of sexual activity, and is liable now to progression, now to recession of vegetative activity, which is precisely the state of affairs in which we have indicated a "habit of growth" as likely to arise. Because of its exposed position, a history of trauma frequently precedes the development of a tumor, and the association has been accorded, especially by the laity, an importance that is probably undeserved. Among primary growths, the epithelial are most important, and consist of fibroadenomas, adenomas, cysts, and carcinomas.

Fibro-adenomas.—These are growths from the size of a cherry stone to that of a walnut, hard, sometimes nodular on the surface, readily shelled out from the surrounding tissue, and on section have a very definite fibrous structure; between the fibrous bands, the glandular tissue protrudes. It will be at once evident that the term fibroadenoma implies that not only is there overgrowth of the fibrous tissue, but also of the gland tissue, and it requires considerable experience to be sure of this on microscopic examination. Pure fibroma of the breast is rare; nearly every fibromatous growth includes in it some glandular structures which necessarily become distorted, pressed, and lose somewhat of their orderly arrangement; there will be all grades seen between a very fibrous growth containing few acini and a slightly fibrous growth showing many acini, yet all alike may be classed as adenofibromas. It is customary to divide these growths into **pericanalicular** and **intracanalicular adenofibromas**. In the pericanalicular form, single gland acini are surrounded by a thick layer of cellular fibrous tissue, while in the intracanalicular form there are papilloma-like projections of proliferated stroma covered by proliferated gland epithelium extending into the lumen of the ducts.

Degenerative or other changes in the structure of the tissues forming these tumors give origin to various modifications such as **adenomyxofibromas**, **adenolipofibromas**, and **adenofibrosarcomas**.

Pure Adenomas.—These are comparatively rare, and are **solid**, or **cystic**. The solid forms approximate somewhat to the fibro-adenomas,

but are distinguished by the extreme increase of glandular tissue.
The cystic form (**cystadenoma papilliferum**) is characterized by the

Fig. 372
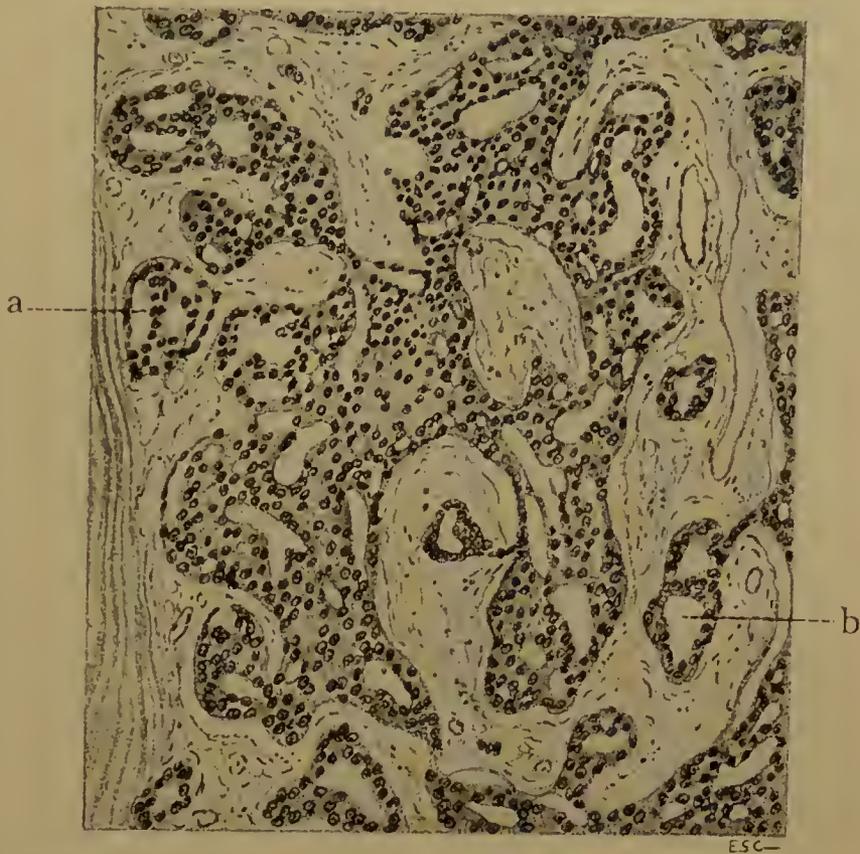
Adenocarcinoma of mammary gland: *a, b*, cancer acini with multiple lumen formation

Fig. 373

Carcinoma of breast infiltrating into surrounding fatty tissue of breast; *a*, fatty tissue of breast
b, small-celled infiltration at outer limit of the advancing growth; *c*, carcinoma.

presence of cysts on the inner walls of which there are small papillomatous or polypoid projections.

Cysts.—If all sorts of cysts are here considered, it is needful to mention milk cysts (**galactocele**) which arise by blocking of a duct during the time when secretion is active. These are true retention cysts. Of another kind are the **involution cysts** found in advanced years; they appear as usually multiple, bilateral, hard small masses, not capable of being shelled out and on section cystic, with variously colored fluid; the state in which these cysts develop is called **chronic cystic mastitis.**

Carcinomas.—1. **Gland Carcinoma.**—This arises most commonly in the fourth and fifth decades as a firm, ill-defined mass in the breast not easily movable apart from the rest of the gland. Frequently, there is a relatively early indrawing of the nipple. The growth becomes more superficial, and as it does so, the skin until now freely movable over the tumor, becomes fixed to it, and carcinomatous masses appear as knobs in the skin. Without complete removal by operation, the carcinoma may spread diffusely through the skin and subcutaneous tissue forming a dense, board-like mass (**cancer "en cuirasse"**). Sometimes the growth breaks through the skin in a fungous mass. Necrosis and ulceration are prone to occur. The lymph nodes nearby are early infiltrated, not only the axillary but the supra- and infraclavicular groups, as well as the pleura, the other breast and the underlying muscle; the secondaries exhibit a tendency to attack the bones.

Microscopically, one may distinguish a soft rapidly growing (**medullary**) form and a hard, slowly growing (**scirrhous**) form, between which are all degrees of variation. When neither very soft nor obviously fibrous, the growth is usually denominated **carcinoma simplex.** The soft tumors are whitish, and exude milky juice, while the scirrhous ones are fibrous, scar-like, and, if in the region of the larger ducts, tend to retract the nipple. Microscopically in a medullary carcinoma the carcinoma cells may be diffuse or arranged in an alveolar or a tubular manner; in scirrhous tumors often in mere lines. The new growth may invade the larger ducts and infiltrate among the fatty tissues; secondary inflammatory reaction is often seen (p. 382). The scirrhous form is modified only in this particular that there is a parallel, strongly progressing process of healing by fibrosis going on, so that in a field the carcinomatous alveoli or tubules may be surprisingly scanty. Psammomatous bodies and colloid change are rare modifications.

2. **Squamous Carcinoma of the Nipple and Areola** (Paget's disease of the breast).—These terms are not exactly synonymous, but **Paget's disease** includes most of the cases; here it seems as if a squamous carcinoma arose from the lining of the larger duct mouths, tending to ulcerate and spread superficially.

Other Growths.—Growths other than epithelial are rather uncommon. **Fibroma** has been referred to; **sarcomas** of the various kinds are seen, as well as **endo-** and **peritheliomas, chondromas,** and **osteomas.** **Melanoma** arises occasionally in the nipple or areola.

CHAPTER XIII

THE MOTOR AND TEGUMENTARY SYSTEMS

THE MUSCLES

THE anatomical muscle is made up of numerous bundles, each of which, in turn, is made of individual muscle cells; the bundles are held to one another by a fibrous tissue network, lodging fat, vessels, and nerves, the perimysium; the individual fibres or cells are similarly held together by the endomysium. The individual fibre cell is differentiated into the fibrils, which carry the transverse striations, the sarcoplasm or cement substance, and the sarcolemma. The fibre is polynuclear, the oval nuclei arranged in rows close to the inner surface of the sarcolemma. The size of muscle fibres differs enormously. The **muscle spindles** are structures distinguished from the other fibres by small size and a thick perimysium; innervated from the sympathetic system, it is thought that they may be the organs of "muscular sense." After death, as soon as a couple of hours in the young, the myoalbumins coagulate, so that in a short time, the muscles are firm and rigid (**rigor mortis**), a condition which passes off after a day or so. The muscle fibre is rigid and shortened.

The muscles are much exposed to trauma and to infection, but they are well protected by the tissue juices and the free circulation. The muscle whose innervation is interfered with is by no means so immune.

Congenital Anomalies.—These are so numerous as to forbid detailed description. **Absence** of a whole muscle or a part, **reduplication, abnor-**

mal origin, insertion, or size include most of the modifications found; muscles may appear in man which are normally found only in some other species. The one muscle whose importance entitles it to special mention is the diaphragm; **defect** of this muscle may vary from a small opening to a lack of almost an entire half, so that the thoracic and abdominal cavities are freely communicative. We have seen at autopsy a huge congenital defect, with many abdominal organs in the thorax, in a man of more than fifty years who had some reputation as an athlete in his younger days; to so much can the body become accustomed.

Circulatory Disturbances.—**Anemia** of the muscles of more than temporary duration rarely occurs apart from generalized anemic states of the body; if there be an obliterative endarteritis of many vessels, the blood supply may be continuously restricted.

Hyperemia occurs in and about areas of inflammation, and in states of passive congestion.

Hemorrhage is usually of traumatic origin; if a large amount of blood be extravasated, a **hematoma** results; this may be absorbed, and the part heal with fibrosis, or may be infected with abscess formation, or a cyst may develop. Smaller hemorrhages (**petechiæ**) are of other origin. They are found in cases of great hyperemia and of great anemia, in very severe toxemias, and bacteriemias, but are less readily seen in muscles than in whiter tissues. **Infarct** is infrequent, because the muscles have a good collateral blood supply; in cases of widespread thrombosis or a general sclerosis of many vessels, infarct may develop, and may even lead to gangrene.

Inflammation.—**Myositis.**—The changes which characterize a slight myositis are those of the connective tissue, the muscle entering into the process only by showing a cloudy or other degeneration. In **suppurative myositis,** abscesses occur by extension from periosteal or cellulitic infections or as a part of a general bacteriemic process, but in this last the muscles escape better than do other solid organs, perhaps because of their activity arousing hyperemia. The abscesses are circumscribed, or there is a diffuse necrosis produced. The process of healing is attended by fibrosis and loss of muscle fibres. We have indicated elsewhere (see p. 200) that so-called rheumatic pains in the muscles may be due to areas of actual inflammation.

Chronic myositis is exemplified by such an inflammation as is seen in arthritis deformans, where there is a progressive thickening of the perimysium and an inflammation of the endomysium with degeneration of the fibres; it may be seen, too, in the neighborhood of any inflammatory process of a low degree of acuity. Here may be mentioned those peculiar cases of myositis which result in the growth of bone in a muscle such as the adductor (rider's bone), and the strange disease called **myositis ossificans.** These it will be remembered are rather examples of metaplasia than of true inflammation, even if, as in the former case, there is a continued irritant at work.

Acute Polymyositis.—This is an ill understood and rare disease, characterized by spontaneous multiple swellings of the muscles of many parts of the body, with loss of motor power, accompanied by urticarial swelling of the skin. There is a marked œdema of the muscles with round-celled infiltration and petechial hemorrhages, and vacuolation of the individual fibres.

Trichiniasis.—This is a widespread inflammation of the muscles due to the presence of a systemic infection by *Trichina spiralis.* The worms obtain entry to the muscles and there encapsulate themselves, appearing as tiny white or gray dots; microscopically the coiled-up worm can be seen in its capsule, which is thick and chitinous; in the muscles around, especially when the parasites are numerous, there is a great cellular infiltration, accompanied by degeneration of the muscle fibres, some of which are degenerated even if not directly attacked by the parasite. The nuclei of the muscle fibres are ordinarily multiplied.

Tuberculosis.—Tuberculosis of hematogenic origin is not very common, but may be part of a generalized infection; the muscles, however, even here seem to be fairly self-protective. Generally the disease is secondary to and in the neighborhood of tuberculosis of the bones and joints, where it takes the form of small or large, caseous areas. The resulting area of suppuration is called a "cold" abscess, the pus from which may burrow for long distances between the muscle bundles, infecting fresh areas as it goes.

Syphilis.—The form usually assumed by syphilis in the muscle is the **gumma**,

FIG. 374

Trichina larva which has penetrated muscle fibre (*b*), while at (*c*) there yet remains a small island of muscular substance which has preserved its striation. (Romanovitch.)

although a diffuse inflammatory form is also seen. Gumma in the muscles reaches its greatest dimensions, and its progress and healing are marked by great fibrous proliferation, atrophy of surrounding and involved muscles often occurring.

Glanders and **Actinomycosis.**—These occasionally give rise to slowly forming abscesses.

Parasites.—Apart from trichina, cysticercus and echinococcus are seen occasionally in the muscles.

Regressive Tissue Changes.—**Atrophy.**—Atrophy of muscles as a whole occurs in old age, or in cases of inanition, excellently exemplified in the marasmus of infants. Not only is there loss of size, but if the process continue long or be extreme, other degenerative changes are

brought about. Atrophy from disuse is seen in cases of long-continued fixation of joints. Equally familiar is the atrophy wrought in infections or cachexias.

Neuropathic atrophy is the form brought about by lesion of the central or peripheral nervous system. Such an atrophy partakes partly of the nature of that from disuse, but there is even more, for the muscle in health is kept in a state of tonus (that is, incomplete relaxation) by continuous rhythmical stimuli of slight force. Somewhat allied to a neuropathic atrophy is that seen in **myopathy (progressive muscular atrophy)**, in which the lesion in the nervous system is not apparent; it is thought that this may be an example of abiotrophy in which the muscle starts life with a less than proper amount of molecular energy. It has little bearing on the pathological condition that the disease in its early stages shows hypertrophy, for this is only apparent, occasioned by intermuscular fatty deposit.

In atrophy from any of these causes there are certain fundamental features to be seen; the fibres are shrunken by loss of contractile substance and one may often observe, laid down in the neighborhood of the nuclei, yellowish or brown granules of pigment (lipochrome) possibly derived from myohemoglobin. The sarcolemma and the nuclei remain unchanged. In simple as opposed to degenerative atrophy, no such granules are to be seen. The deposit of increased fat in the perimysium is a frequent accompaniment of all forms.

Cloudy Swelling.—As a result of infections and intoxications, there appear in the muscle cell dully refractile granules which veil the striation; these are soluble in acetic acid; such a state often progresses apparently to **fatty degeneration,** in which the fat droplets may be seen in rows; as they coalesce, the striations disappear and the cellular structure and even the nuclei are destroyed.

Waxy Degeneration (Zenker's Degeneration).—This is observed especially in the rectus abdominis and adductors in typhoid fever, less often in other infections and in trauma. The muscle is parboiled looking, pale and waxy in appearance. Microscopically, entire fibres or parts of fibres are seen to be ill-stained and of a uniformly waxy appearance, the contractile substance appearing to have undergone a coagulation necrosis. Transverse rupture of the fibrillæ appears to occur, although some hold that this is an artefact. The occurrence of small hematomas, however, is strongly against this supposition.

Progressive Tissue Changes.—The regenerative processes of muscle have been discussed elsewhere (p. 313). **Hypertrophy** of a muscle from increased work in the presence of adequate nutrition, consists in a broadening and lengthening of the individual cell. Debate still exists as to whether or not a numerical increase of fibres occurs.

Tumors.—Primary tumors of muscle are not very common, and the **fibromas, myxomas,** and **angiomas** that are observed, as well as the lipomas, arise from the connective-tissue structures, the peri- and endomysium, etc. Rhabdomyomas originating from the muscle cells are singularly

rare. **Sarcomas** of various kinds may be found, and while we have seen **rhabdomyosarcoma** in the trout, its occurrence in man is little known. Secondary sarcomas and carcinomas are not common, save by extension.

THE TENDONS AND TENDON SHEATHS

The tendons are relatively avascular bundles of strongly united parallel fibres, held together by a small amount of connective tissue which carries the blood vessels, the interfascicular tissue, and which forms an external covering, the perifascicular tissue. The tendon is enclosed in a dense fibrous capsule, between which and the tendon is a space filled by synovial fluid which serves as a lubricant. The tendon sheath cavity is thus one of the synovial spaces, and as such is very like the joint cavities and the bursæ. By reason of their little vascularity they are not prone to infections of a primary nature.

Inflammation. — **Tendinitis** and **Tenosynovitis** (Tendovaginitis). — Despite the name tendinitis the tissue of the tendon practically plays no part in inflammatory processes, which concern chiefly the interfascicular tissue and the sheath.

Acute Tendinitis and Tenosynovitis.—This is an exudative inflammation with fibrinous, serofibrinous, or purulent exudate. The less severe forms may evidently arise as primary diseased states in rheumatism, and from trauma, while the purulent forms are usually by extension, or by infection from penetrating wounds, rarely hematogenously. With a **fibrinous** exudate, "dry tenosynovitis," the fibrin forms a thin layer between the moving surfaces, and motion gives rise to crepitation. It is quite often seen in the extensors of the thumb and hand. The **serofibrinous** form, in which there is some fluid exudate in the sheath, is oftenest seen in the flexor tendons of the hand; when absorption of the fluid occurs, the healing process, as in the pleura, may be accompanied by the formation of adhesions between tendon and sheath. These may greatly limit movement, until in time by the continuance of movement they become lengthened, thinned, and they may finally disappear. **Purulent tenosynovitis** is characterized by a purulent exudate, and its danger lies in the fact that there may be necrosis and digestion of the interfascicular substance with separation of the tendon into its component parts and necrosis even of these.

Chronic Tenosynovitis may result in much thickening of the wall and secretion of fluid exudate which distends the sac (**hygroma of the tendon sheath**). The organizing process and the overproduction of tissue in such a case may lead to the formation of polypoid and papillate bodies which become separated off from the surfaces, and, being free in the sac, are called "rice bodies." These are merely hyaline masses of degenerated cells. **Calcareous deposit** may occur as a result of a long-continued inflammation.

Tuberculosis.—Tuberculosis of the tendon sheaths can be primary, but is usually secondary to disease of a joint or bone nearby. It may

consist of a diffuse inflammation with rapid growth of granulation tissue which fills the cavity and covers the tendon; the interfascicular tissue of the tendon may become infected and the tendon increase in size. The soft granulation tissue readily caseates and a suppurative process may ensue and finally burst through the superficial structures. More rarely tuberculosis may show itself as circumscribed overgrowths of slow progression and accompanied by much fibrosis. Finally, the "rice bodies," spoken of above, may bethe product of a tuberculous process.

Syphilis.—Syphilis may appear as a more or less acute tenosynovitis in the earlier stages of the infection; later, gummas occur on the wall of the sheath.

Fig. 375

Chronic bursitis, bilateral.   (McGill Pathological Museum.)

Gout.—A deposit of urates occurs in the tendons and the sheaths, with sometimes a necrotic process leading to disintegration, while again there may be a proliferation of connective tissue and a corresponding increase in size of the tendon.

Progressive Tissue Changes.—Tumors.—Sarcomas of the tendon and of the tendon sheath have been seen; **lipomas** occasionally arise in the sheath.

Ganglion.—The so-called "ganglion" arises from tendon sheaths, as from joints, as a cyst with a fibrous wall, containing thick, gelatinous synovial fluid; it is frequently seen on the back of the wrist, **carpal ganglion,** and consists of a hernial pouch whose wall is made of the distended tendon sheath.

THE BURSÆ

These are fibrous sacs containing synovial fluid, and while some are constant and preformed, others arise where tissues are subjected to pressure, such as is caused by the play of a tendon on a bone. They become lined by a definite endothelium, and being perfectly analogous to the tendon sheaths, they are subject to much the same processes of disease. Fibrinous, serofibrinous, and purulent exudates occur in **inflammation** of the bursæ, under conditions similar to those under which tenosynovitis occurs, with the difference that the bursæ are more exposed to trauma than are the tendon sheaths. **Chronic bursitis** is characterized by much thickening of the walls and a considerable amount of exudate, so that a large swelling may be produced at the site of the bursa (**hygroma**). "Housemaid's knee," "miner's elbow," and "weaver's bottom" are all well-known forms of bursitis. **Tuberculosis** affects the bursa usually as a diffuse granulomatous affection of the lining membrane.

Sarcoma, endothelioma, fibroma, and **myxoma** of a bursa have been found, but none of these are common.

THE BONES

It is worth stating, that rigid as is its nature and apparently fixed, bone is throughout life undergoing a steady constant process of absorption and reformation according to the needs of the economy. There is, indeed, no more excellent example of the economical use of material than is afforded by the normal structure of bones, particularly the long bones. Just as the engineer has determined that the hollow steel cylinder is capable of standing greater weight and greater strain than a solid column formed of the same amount of material, so the long bones are formed not as solid masses of calcareous matter, but as cylinders, and what is more, they expand at their extremities; instead of being solid we find that the bone is laid down as a lattice-work of "struts" whose arrangement is finely adapted to bear stresses upon the bone in particular directions. Now these stresses may vary with the changing weight of the individual and with the growth of the different parts, and as a consequence we find that these "struts" undergo alteration to adapt them to the altered stress. On one aspect we may find removal of the bony substance through the agency of osteoclasts; on the other side of the same lamella there may be a simultaneous new formation of layers of bone through the agency of the osteoblasts. In an exaggerated condition we may find these simultaneous processes of absorption and new formation occurring in diverse pathological disturbances.

Abnormalities.—In true **dwarfism,** as again in true **giantism,** the bones share the general abnormality of development of the tissues.

There are, however, other dwarfs in whom the bony development is not proportioned. One group, for example, exhibits a marked shortening of the limbs; such dwarfs are examples of **chondrodystrophia foetalis** (**achondroplasia, micromelia**). There has been much debate as to the underlying process in this condition, but the disease may be regarded as a fœtal rachitis. It is found that the periosteal formation of bone proceeds in a normal manner, but at the junctions of epiphyses and diaphyses the chondriform development is imperfect, and as a result the bones do not grow adequately in length. A similar process, involving the skull, is to be seen in those bones which are of chondriform origin, that is, in the bones of the base. As a result of their imperfect development the base becomes markedly shortened and the bridge of the nose sunken in; and as the nasal bones themselves also are of chondriform origin the nose is short, flattened, and of negroid type.

A somewhat similar arrest of development of bony growth is seen in cretins (**cretinism**), there associated with congenital inadequacy of the thyroid; the bony skeleton in this condition shows more particularly a shortening of the limbs, something of the type seen in chondrodystrophia but not so extreme, while there is the same indication of arrested development of the chondriform bone formation of the skull base as is presented by the nose. With this, however, there is more marked general arrest of mental and sexual development than is presented in chondrodystrophia.

Yet another type of congenital bone disease is seen in what is termed **osteogenesis imperfecta**, although many other names have been given, as **fragilitas ossium, osteopsathyrosis**, or **myeloplastic malacia**. In this condition during early life and, indeed, during intra-uterine life the bones show an abnormal liability to fracture. In a case in our collection, reported by Klotz, the body of the newly born infant showed over a hundred such fractures. Associated with this there is marked deformity and shortening of individual bones and of the skeleton in general. This is, strictly speaking, more closely allied to rickets than is chondrodystrophia; there is, namely, abundant preparation for the formation of bone, in the shape of well-developed cartilage formation, only there is a failure both in the periosteal and chondriform metamorphosis into true bony tissue. Even in the shafts, the periosteum may give origin to fibrous tissue rather than bony lamellæ. This defective formation may be so extreme that large areas of the calvarium may remain purely membranous.

Circulatory Disturbance.—The very rigidity of the channels within the bone substance prevents extreme alterations in the blood supply. The periosteum, however, is liable to exhibit more pronounced changes, **active hyperemia, passive hyperemia**, etc. More important, there may be extensive periosteal **hemorrhages**, either traumatic or as a result of disease. Closely allied to the traumatic must be mentioned a most striking form of periosteal hemorrhage, viz., the **cephalhematoma** of

the newborn. Here as a consequence of unduly prolonged presentation of the head in the cervical portion of the uterus, and of the great compression exerted upon the body of the infant by the contracting uterus, the extreme congestion of the vessels of the calvarium leads to rupture of the same as they pass into the overlying pericranium, with hemorrhage between the two layers, and an accumulation of blood the size of half an orange may result. This hematoma may undergo absorption, but if the process of removal is slow, a ring of bony growth may occur at the periphery.

Infarct.—The predisposition shown by young children to osteomyelitis originating at the ends of the long bones is usually ascribed to the active vascularity with new vessel formation presenting itself in the neighborhood of the epiphyseal line, the new vessels here becoming the seats of bacterial emboli. We have stated elsewhere that we doubt whether such emboli are truly primary; rather we imagine that individual bacteria arrested by the endothelial cells multiply and set up a focus of inflammation with thrombosis. Whether actual infarcts occur is a matter of controversy. The appearance seen in many cases of tuberculosis of the ends of the long bones strongly suggests infarct formation; wedge-like areas of necrotic bone may be detected having their bases immediately beneath the cartilage, but here it may well be that there is not primary embolism but obliteration of the nutrient artery in consequence of perivascular tubercle formation and the associated endarteritic changes. Extensive necrosis may occur where, either through trauma or through accumulation of inflammatory products, or of blood, the periosteum becomes separated from the underlying bone and the nutrition of the latter is cut off.

Inflammation.—According as the inflammation involves the periosteum and the surfaces of the bone, or the substance of the bone and the medullary cavities, so do we distinguish between a **periostitis**, an **osteomyelitis** or, inasmuch as one process, if severe, inevitably leads to the other, a general **osteitis** or **panostitis**.

The study of these conditions is complicated by the fact that whereas an infective agent, acting intensely, leads to necrosis and absorption of the bone substance, in the areas of surrounding hyperemia there is set up coincidently a productive process leading in the deeper parts of the bone to increased thickness of the lamellæ and greater density of the tissue, and on the surface to the formation of new bone layers or of osteophytes, irregular processes of new bone. In extreme cases the intensity of the inflammatory process and the presence of tension may lead to the necrosis of relatively large masses of bone, which undergo a very slow process of absorption while simultaneously the periosteum gives origin to new bony layers. As a result we obtain a **sequestrum** surrounded by an **involucrum**, with associated thickening and deformity. Usually in these cases the purulent fluid surrounding the sequestrum makes its way along the line of least resistance, through some area of weakened periosteum, into the subcutaneous tissues and so to the surface, giving rise to one or more **sinuses**.

Periostitis.—Acute periostitis may be of two forms, simple and suppurative. The former shows itself in non-infective traumatic infections and in infections of low virulence, and is characterized by a mildly acute course with infiltration and subsequent thickening of the periosteum, stimulation of the genetic layer to active bone production resulting in a local increased production of bone in the form of osteophytes or nodular thickening. **Suppurative periostitis** is much more acute, and involves a larger area and shows itself as an accumulation of pus cells within the periosteum and then between the periosteum and the bone. This accumulation of pus tends to extend around the shaft of the bone laterally in all directions, inasmuch as the density of both periosteum and bone prevents extension either outward or inward. There is thus great tendency for the nutrition of the bone through the periosteum to be cut off, as also for the process to extend to the joint setting up a suppurative arthritis. With the continuance of the disease, the periosteum at one or other point may undergo atrophy and erosion, the pus thus extending into the surrounding tissues and setting up a periosteal suppurative process. So also in some cases the process extends along the vessels into the marrow, inducing a **panostitis**. Such suppurative periostitis may be brought about in two ways, either as the result of an infective traumatism or, as happens not infrequently in young children, as a hematogenous or cryptogenetic process. The organisms associated with the process are most frequently the pyogenic cocci, and such bacilli as B. coli and B. typhosus. The latter is especially apt to set up a somewhat restricted and localized suppurative periostitis, sometimes showing itself long after the acute infection has passed. In the young, there is a peculiar liability for this suppurative form of disease to extend along the epiphyseal lines and lead to separation of the epiphysis from the shaft of the bone.

Osteomyelitis.—In this condition the primary infection occurs in the marrow of the bones, and may be set up by the same organisms as induce in other cases periostitis. Like periostitis, the condition is most common in the young and during adolescence, while the long bones are those most frequently affected. As already indicated, not infrequently the disease begins as an infective **epiphysitis.**

The ordinary course of infection is modified in the case of the bony substance by the unyielding nature of the framework; the congested vessels cannot throw out much exudate or, more correctly, the exudate and infiltration of leukocytes react upon the vessels themselves favoring thrombosis and the rapid production of relatively large areas of necrosis. Thus **caries** or necrotic softening with absorption and more extensive necroses of bony tissue is a common accompaniment. We have already referred to the results of these processes in the production of sequestra; so, again, the inflammation is very apt to extend to the periosteum inducing suppurative periostitis, periosteal perforation and the formation of fistulæ The process, if very acute, gives rise to a generalized bacteriemia or pyemia resulting in death; if less acute, is followed by various

stages of reactive development of new bone, although often from the enclosed nature of the foci of suppuration the acute stage passes on to the chronic or latent form of osteomyelitis, with tendency toward acute exacerbations from time to time, over, it may be, years.

Chronic Periostitis.—Various forms are described. As already indicated, continued mild inflammation of the periosteum leads to bony overgrowth, and the formation of osteophytes—**periostitis ossificans.** The periosteal overgrowth of bone after fractures is of this nature; so, also, the bony overgrowths through irritation induced by neighboring tumors or inflammation of overlying structures, as is well shown in the nodular overgrowth of the tibia under a chronic ulcer. To the commonest form of chronic periostitis, viz., the syphilitic, reference will be made later. A remarkable type of periosteal inflammation, the **periostitis albuminosa,** has been described by Ollier in which a thick serous fluid containing albumin, and a few pus corpuscles and some fibrin, collects between the periosteum and bone; it appears to be of mildly infective origin, and differs merely in degree from the more acute suppurative periostitis.

Chronic Osteomyelitis.—According to the virulence or concentration of the infective agents, so do we find two processes manifesting themselves in cases of long-continued inflammation of the bone substance, viz., **rarefaction,** or **osteoporosis** and **condensation,** or **sclerosis.** **Rarefying osteitis** is evidenced by the progressive absorption of the bony lamellæ. The marrow becomes increasingly vascular, and through increased osteoclastic activity the compact bony tissue undergoes reduction until it assumes a loose spongy appearance. According to Ribbert and others, in these inflammatory processes the presence of osteoclasts is not essential, but ordinary leukocytes possess the capacity of causing absorption of the bone, as clearly happens when the bone has already undergone necrosis, as in a sequestrum.

Condensing osteitis occurs, as already stated, where the irritation is not so intense. One of two events may occur; either there is evidence of increased osteoblastic activity so that the lamellæ undergo progressive thickening and the marrow spaces become correspondingly reduced, or the marrow first becomes less cellular, shows an increased fibrosis, and the cells of this fibroid tissue undergo metaplasia, becoming bone corpuscles. In this way, save for a small space around the central vessels, the whole of the marrow may become converted into dense bone. If at the same time there is progressive periosteal new development the shaft may become thickened to twice its normal diameter, and the central marrow may be completely replaced by solid bone. It is this secondarily formed compact bone which, from its extreme density and likeness to ivory, has been described as **eburnated bone.**

We shall discuss the so-called **osteitis deformans** among the regressive changes.

Specific Inflammations.—The bone is peculiarly liable to be infected in both tuberculosis and syphilis, and to present characteristic modifications.

Tuberculosis.—Tuberculosis may show itself either as (1) of primary periosteal origin, or as (2) a form of specific osteomyelitis, or (3) a generalized miliary tuberculosis. The last is relatively unimportant, inasmuch as death occurs before any grave change has ensued in the bones. Periostitis, also, is apparently not of first importance; it is seen particularly in the ribs. By far the most important form is **tuberculous osteomyelitis.** Certain bones are particularly apt to be affected, notably the ends of the long bones, the femur and the tibia, and the vertebræ. Less frequently the calvarium and the phalanges may be involved. Tuberculosis of the spine and the long bones is practically of the very greatest importance, and this fact is due, to a large extent, to the function of the parts concerned, namely, that the weight-bearing of the body is vested in them; thus, the tuberculous disease is assisted by pressure at all times during which the upright position is maintained, and the lesion begun by the disease is increased by the pressure. This osteomyelitic process in the long bones originates with great rarity in the shaft, save in connection with the phalanges of children (**spina ventosa**), but almost always in the epiphyseal ends, and this in children and adolescents. The process begins by the formation of a conglomerate tuberculoma, with surrounding development of granulation tissue in the medullary spaces and absorption of the bone substance. Two orders of change may appear; either the tubercles may show little tendency to caseation and granulation tissue formation may predominate or, more frequently, the mass of tubercles caseates while simultaneously new tubercles form in the surrounding medullary spaces with, as a result, a progressive and spreading caseous change, and accompanying destruction and rarefaction of the bone tissue. We have already pointed out how economically the normal bony substance is laid down in relation to the strain it is called upon to bear, and, therefore, if there be any considerable area of rarefaction and destruction without corresponding overgrowth in the neighborhood, the inevitable result is that the bone gives way and becomes distorted. This distortion is peculiarly well seen when the head of the femur is the part involved. At this process advances, it is apt to extend to the cartilaginous joint surface and with erosion of the cartilage through lack of nutrition, the joint now becomes infected and tuberculous arthritis is set up. A similar osteomyelitis involving the vertebræ begins within the substance of the bodies, often as scattered foci, which as they enlarge by formation of new tubercles at their peripheries, tend to fuse and give origin to large areas of caseation and caries, the latter so soon as the area reaches the periosteum and interferes with nutrition. When the process extends to the intervertebral disk it causes a rapid destruction of the same with extension of the tuberculous process into the neighboring body. Here the inevitable result is that the softened vertebral bodies become compressed under the weight to which they are subjected and **kyphosis** or angular backward curvature results. Whether as a result of this compressing force or from the

comparatively thin periosteum covering the vertebral bodies, there is a pronounced tendency for the softened caseous matter formed within the vertebral body to escape into the immediately overlying tissues, in which it may travel great distances by unexpected courses, inducing what is called a **cold abscess**. The abundant contents of such are not constituted of true pus but of diluted cheesy matter with a small proportion of leukocytes and lymphocytes unless a secondary infection has occurred, when there is a greater predominance of leukocytic

Fig. 376

Skull showing syphilitic caries. (McGill Pathological Museum.)

elements. The term *cold* doubtless refers to the lack of surrounding inflammatory manifestations, such as the active hyperemia of the skin. A cold abscess is usually lined by a layer of necrosing or caseating tuberculous tissue. Similar periosteal extension of the process may show itself where the upper end of the femur is involved ("**hip-joint disease**") or when the knee is affected ("**white swelling**").

Syphilis.—The bones are almost always involved to a greater or less extent in cases of congenital syphilis and are frequently the seat of lesions in the acquired disease. As with other organs we can distinguish diffuse and circumscribed lesions. The circumscribed lesions or **gummas**

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may develop as a comparatively late manifestation and then either in the periosteum or in the medulla. They are slowly progressive and cause little destruction as compared with the tuberculous; rather, in general, they induce a surrounding, almost compensatory sclerosis,[1] and, in the case of the periosteum, active new bone formation, the result of which is, very frequently, a localized nodular thickening and overgrowth in their immediate neighborhood. But more particularly in the calvarium, the obliteration of the vessels leads to necrosis and extensive localized destruction (**caries**). Unlike the tubercle bacillus the spirochete has no special seat of election in the bones; the gummas may be diffusely scattered through both the diaphysis and the epiphyseal region.

The diffuse form of syphilis is characterized by increased bone production (periosteal) and sclerosis, so that the long bones, for example, become greatly thickened and condensed. With this, there is a liability to the formation of exostoses, which may be seen in the long bones but more particularly on the inner aspect of the calvarium. As a result, the vault of the skull is found greatly thickened, so dense as to be sawn with difficulty, and on its inner aspect there may be a massive development of close set nodular osteophytes.

The characteristic disturbance of congenital syphilis is what may be termed **osteochondritis**, affecting the layer between epiphysis and diaphysis of the long bones and the osteochondral junction of the ribs. We find, either that there is an undue formation of the cartilage, which undergoes calcification without proper bone formation, or this calcification of the cartilage is accompanied by an excessive granulation tissue sending processes into the epiphysis. In either case the fine line of demarcation between epiphysis and diaphysis is replaced by a broad yellowish band, often irregular, which consists of cartilage which has not gone on to proper bone formation. As a result there is to be observed a distinct liability to separation of the epiphysis under very slight provocation. The condition shows itself in the first few weeks of life and recovery may follow. At a later period in these congenital cases, there may develop a syphilitic periostitis of the same order as that seen in the acquired disease. **Gummas** are rarely seen in the newborn but soon after birth the gummatous process affecting the septum nasi may lead to its destruction with the development of a "saddle-back" nose. This process may lead in addition to perforation of the hard palate or be accompanied by atrophic rhinitis and ozena.

Other Infective Granulomas.—Of the other infective granulomas, attention may be called to the involvement of the bones, especially the lower jaw, in a primary **actinomycotic** process. Unlike what is seen in cattle, the condition in man is rarely primary in the bone itself. In connection with **leprosy** of the anesthetic variety it must be recalled that the phalanges are apt to undergo a rarefying osteitis and absorption. Harbitz considers this to be due to a trophoneurosis.

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[1] This word is here used in a sense differing from that which it bore in the chapter on the nervous system. It bears its true meaning of a hardening process.

Regressive Changes.—Atrophy.—We have already referred to senile changes in the bone marrow; in addition, with old age, the bony substance undergoes progressive absorption and regression so that the bones become light and very brittle. Such senile atrophy is especially seen in the flat bones, including the lower jaw, but affects also the long bones and exhibits a combination of two processes, viz., (1) superficial absorption, the so-called **concentric atrophy,** whereby the diameter undergoes reduction and (2) **osteoporosis** or Haversian atrophy or lacunar resorption, the Haversian canal becoming distinctly enlarged by absorption of the superficial layers of the lamellæ. The above-mentioned atrophy seen in anesthetic leprosy is an extreme example of this order of change; closely allied is the atrophic change in bones, encountered in syringomyelia and tabes dorsalis. Other examples are seen in disuse atrophy, and the atrophy and absorption secondary to pressure (though here also there is inflammatory absorption of the tissue whose nutrition has been reduced).

Halisteresis.—Such simple atrophy must be distinguished from halisteresis in which the absorption of the bone is preceded by solution and absorption of the bone salts. This latter process is dominant in certain remarkable disorders, notably in **osteomalacia** and in many cases of so-called **osteitis deformans,** between which disorders there are many points of relationship.

Osteomalacia is a condition most frequently described in females and then in association with pregnancy or lactation, but it may show itself also in adults either male or female. It is apt to affect the whole bony framework and may show itself first in particular orders of bones. Notably in the female, the pelvis is apt first to show disturbance, and, through the loss of bone salts and softening, there may be developed striking deformity, the acetabula being pushed upward by the weight of the body, the blades of the ilia pushed outward so as to become more horizontal, and the pelvic outlet correspondingly diminished. With this there may also be great softening of the bodies of the vertebræ with lordosis, kyphosis, and scoliosis, and the long bones may be found so softened that they can be easily cut with a knife. The process may go on until there is practically complete absence of bone salts in individual bones, but in general, along with the absorption, there are evidences of attempted adaptation or regeneration so that, for example, in a long bone which has undergone deformity, while on the convexity of the curve the bone is rarefied, there is thickening along the concavity, only here the new bone formation is imperfect. Microscopically the bone presents a very characteristic appearance; the Haversian canals and the medullary spaces are enlarged and comparatively impoverished in cell contents; the lamellæ may be wholly devoid of bone salts, or more frequently the central layers still contain these salts and are surrounded on either side by layers of somewhat hyaline **osteoid** substance, devoid of salts, but taking on a differential color with various stains, being especially strongly stained by carmine. The process may

be progressive or may be arrested and once more the lamellæ attain their due amount of calcareous material.   Accompanying the development of the process there is a marked increase in the excretion of cal-

FIG. 377
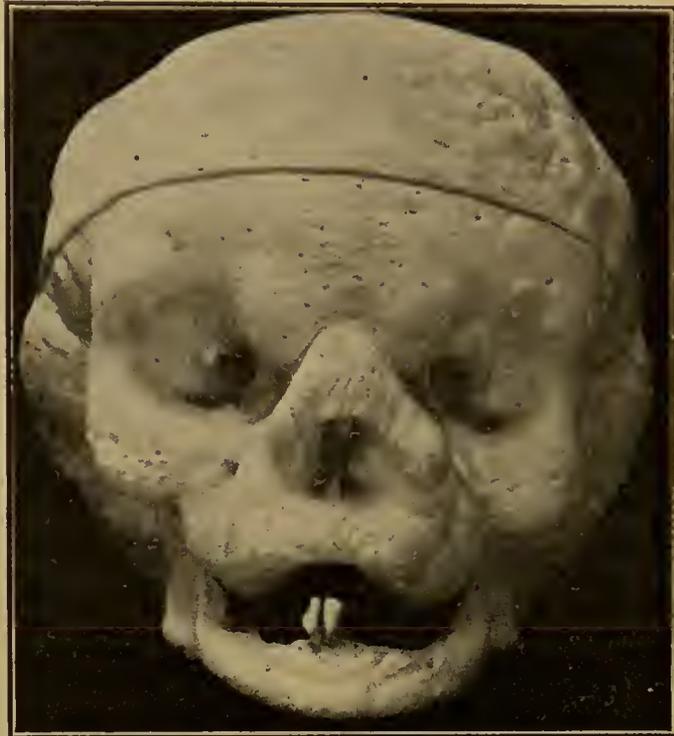
Deformity of the skull in Paget's disease.   (Max Koch.)

FIG. 378

Same skull seen from within.   (Max Koch.)

careous salts in the urine, the milk, and even the feces. As to the origin of the disease, little is known; its frequent association with gestation suggests that here we may deal with some disturbance of the ovaries as organs of internal secretion.

Osteitis Deformans (*Paget's Disease of the Bone*).—This is a progressive-condition affecting the bony skeleton, most often of elderly individuals, not necessarily affecting all the bones but telling more particularly upon the long bones (notably the tibia), the skull, and the vertebræ. Cases are on record in which a single tibia or a single femur has been involved; the affected bones show progressive irregular thickening combined with distortion and exaggeration of the normal curvature. There appear to be two if not three stages in the process affecting the bone. First, there is halisteresis resembling that seen in osteomalacia but followed or accompanied by a much more pronounced periosteal and even medullary new growth of osteoid tissue. This new tissue does not gain proper calcification, but on the contrary is apt in turn to become the seat of absorption with enlargement of the medullary and Haversian canals. Associated with this, as a third stage, the medulla undergoes characteristic and diffuse change. In place of being fatty or abundantly cellular, it becomes fibroid. Von Recklinghausen regarded this change as of an inflammatory nature, and spoke of the condition as **osteomyelitis fibrosa**. We can find no evidence of this inflammatory stage and regard the process as metaplastic. This "*Fasermark*," or fibroid medulla, is apt to show areas of degeneration with cyst formation, but in a certain proportion of cases exhibits a further diffuse metaplastic change, becoming abundantly cellular with a tendency to the formation of new osteoid lamellæ and what might be termed a blastomatoid formation of new bone-producing tissue, which, in its turn, may again give place to infiltrative localized growth of sarcomatous nature.[1]

Close upon 10 per cent. of recorded cases exhibit this eventual local malignancy. With this general osteoid change and softening of the bone there may be extraordinary deformities produced. As to the causation of this disease nothing definite is known, but the diffuse type of the change, the known association between the pituitary, the parathyroids, and the calcium metabolism of the body, lead us to the belief that here we deal with another of the disturbances associated with want of balance between the organs of internal secretion. A few cases have been recorded in which lesions of the pituitary and thyroid have been associated with the condition.

Rickets (*Rachitis*).—This is a disease affecting the skeleton in general and manifesting itself after birth, most often in the first and second years, although it may continue as an active process into early childhood. Its effects are shown most characteristically in connection with the long bones, the ribs and costochondral junctions, and the skull. The

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[1] This occurred in a case very thoroughly studied in our own laboratory by the late Dr. Elsie B. Wilkie.

dominating feature of the disease is an excessive preparation for the formation of cartilaginous bone followed by defective deposit of bony salts whether in chondriform or membraniform bone. This leads to the development of bones which are imperfectly rigid and liable to exhibit irregular and excessive curvature with deformity, along with "green-stick" or partial fractures. The condition, however, is not permanent and the deformed bones eventually gain a normal or more than normal deposit of calcareous salts, although the deformity may persist through life. The process may involve the spinal column leading to curvature, and through the soft condition of the ribs they yield to the forces acting upon them, so that the chest becomes flattened in the anterolateral regions and the sternum forced forward, causing what is known as "pigeon-breast," At times the anterior curve of the ribs is markedly increased, so that the lower end of the sternum forms

Fig. 379

Funnel-breast, showing depression of lower part of sternum.   (Bier.)

the deepest part of a depression with sloping walls formed by the cartilages and ribs—"funnel-breast." The rachitic "rosary" is a swelling of successive regions of junction of ribs with sternal cartilages; while this can be felt from without during life, it is most pronounced on the inner aspect of the thorax. The joints of the limbs appear enlarged relative to the shafts of the bones. The forehead may take on a curiously square appearance, due to what is known as **craniotabes**, with thinning of the cranial bones, most marked in the parietal and occipital bones, and there may appear hyperplastic "bosses" of the frontal and parietal bones. With this there is delayed union of the sutures, so that the anterior fontanelle may remain open until the beginning of the fifth year. Dentition is late and the teeth fall an easy prey to carious change.

As to the causation of rickets, little is known with any precision. It is not of syphilitic origin, although it may occur in the subjects of congenital syphilis; it is most often found in city children; lack of fresh

air and sunlight, unsanitary surroundings and deficient nutrition are strong predisposing factors, although of two children subjected alike to these influences one may become rickety, the other not. Morpurgo, confirmed by other Italian pathologists, has isolated what he regards as the specific organism inducing the condition. The time has not come to state with certainty that this is an infective disease.

If we examine the epiphyseal end of one of the long bones, the line of cartilage between epiphysis and diaphysis is found greatly thickened and finger-like processes of new cartilage extend deeply into the marrow, giving an irregular line of demarcation. In the deeper portions these columns of cartilage cells, instead of giving place to true bony lamellæ, pass into an area of osteoid tissue, poorly supplied with bone salts. Here and there masses of the cartilage may become isolated and surrounded by the osteoid tissue. This zone of osteoid tissue passes more deeply into the medullated bone than normal, but gradually gives place to bone proper, although there may be an intermediate zone in which the central areas of the lamellæ contain bone salts while the peripheral portions are devoid of these salts.

Between the osteoid lamellæ are relatively wide channels filled with a marrow, containing sparse marrow cells proper, but showing spindle cells and fine fibrils, a more fibrous marrow than normal. This may undergo a direct metaplasia into osteoid tissue. With progressing age this osteoid tissue exhibits a more and more complete deposition of calcareous salts until the whole of the lamellæ may take on the normal appearance, and the bones become of almost ivory hardness, with small Haversian canals. Periosteal bone is not laid down regularly, but while its development is arrested in certain areas it is apt to be excessive in others, osteophytes being produced.

Infantile Scurvy (*Barlow's Disease*).—This disease is one of recent observation, it having been unrecognized prior to the employment of pasteurized milk and various sterilized milk preparations. It is unknown in children fed upon the mother's milk, and presents itself first as an exquisite tenderness of the limbs so that the child screams upon being moved. Upon post mortem examination this tenderness is found to have its cause in an acute congestion of the periosteum with the development of subperiosteal hemorrhages; hemorrhage in the medulla may also be present. The nutrition of the bones is gravely affected: they are of lighter build than normal with a tendency to fracture and curvature. Hemorrhage may occur in other organs and recall that phenomenon associated with scurvy. As in that disease, so here, the exhibition of fruit juices is found to arrest the progress of the malady; there is, on the other hand, a certain likeness to rickets, *e. g.*, softening and curvature of the bones.

Progressive Changes.—The important subject of the repair of bone with callus formation has been touched upon by us on p. 308; as also we have dwelt to a considerable extent upon the different orders of primary tumors of bones in the sections upon myelomas (p. 355) and

osteomas (p. 353). Here we need only repeat that it is in very many cases difficult to draw the line between local **hyperplasias** and the true tumors of bone, and that true primary benign tumors are really infrequent, most of the osteomas being hyperostoses.

Tumors.—We thus recognize circumscribed hyperostoses—**exostoses**, localized bony formations of periosteal origin projecting from the surface of the bone, and **enostoses**, originating from the spongiosa. Of similar nature are the **ossifying ecchondroses**, nodular overgrowths projecting from the bone in the regions where there had been previous chondriform developments, notably in the region of the epiphyses. These have a superficial layer of cartilage and often a small bursa over their free aspect (**exostosis bursata**), and may be multiple.

Other benign connective tissue overgrowths of the bone are rare, if we leave out those originating from the periosteum. If we include these, fibromas of the bone are occasionally met (**fibrous epulis**), as also nasopharyngeal polyps of fibromatous nature, originating from the periosteum of the base of the skull or the walls of the nasopharynx. Pure **myxomas** are very rare, **myxo-chondromas** and **myxo-sarcomas** more common.

Tumors originating from the bone marrow may be of the relatively benign type, so-called **giant-celled sarcoma**, which we regard strictly as an osteoclastic **giant-celled myeloma**.

Myeloma multiplex may be regarded as a diffuse blastomatoid overgrowth of the marrow, and may be composed of more than one type of marrow cell (see p. 355). Simple **angiomas** are rare, but there are a few cases of a remarkable **hemangio-endothelioma** on record, involving particularly the bones of the calvarium and showing channels filled with blood and lined by an almost cubical endothelium. Intermediate tumors of the nature of **osteosarcoma**, **osteoid sarcoma**, **chondro-osteo-sarcoma**, and **chondro-sarcoma** are to be found. The most frequent form of bone tumor is malignant and sarcomatous. We distinguish **sarcomas** of periosteal and of endosteal origin. The former produce large, oval masses of new growth surrounding or spreading over the surface of the affected bone; they may be round or spindle-celled. What is more, a tumor arising periosteally may invade the shaft of the bone causing its absorption. These are more frequent than the central sarcomas, which, again, excluding the giant-celled myelomas, may be round, spindle, or mixed celled. These central sarcomas are liable, by progressive absorption of the surrounding bone, to give origin to spontaneous fracture.

These malignant sarcomatous tumors of bone show certain features in common, viz., they are apt to be extremely vascular and may present extensive hemorrhages, or later these hemorrhages may give place to cysts, or, again, may be accompanied by extensive necrosis; the growths may spread into the surrounding soft parts, and the nearby lymphatic nodes, and frequently afford metastases in the lungs.

As to secondary growths, many cases are on record in which thyroid tissue has been found forming circumscribed tumors within the bones.

While primary epithelial growths do not exist, it is striking how certain carcinomas of particular organs show a predilection for extension into the bones. This is notably the case with prostatic, and, to a less extent, with mammary cancers. So, also, is it with the mesothelial hypernephroma which may afford metastases in bones either by extension or at a distance.

A useful distinction between periosteal and endosteal sarcomas is that the former, while they may have a framework of radiating bony spicules, possess no covering layer of bone; the endosteal sarcoma, on the contrary, as it expands and causes the absorption of the bony tissue in its neighborhood is apt for long to remain covered by a layer of periosteum which layer, no matter how great the expansion of the tumor, continues to give origin to bone and thus this form of sarcoma is apt to be covered by an imperfect thin bony layer, so thin that on pressure it affords an "egg-shell crackle."

Cysts.—Cysts may originate in bone either in connection with new growths or with osteitis deformans as the result of localized necrosis, with or without hemorrhage, and subsequent autolytic absorption of the necrosed matter. Parasitic cysts are of great variety. In connection with the jaw cysts of another order may develop, viz., the **dentigerous cysts**, formed around accessory and imperfect tooth germs; they may be either uni- or multilocular, the latter being of the nature of cystadenoma.

THE JOINTS

Each joint consists of a cavity containing a special fluid—the synovial fluid—interposed between two or more bones which in this way become capable of moving one against the other. This cavity extends somewhat beyond the apposed surfaces of the bones, and is lined by an endothelium composed of one layer of cells, which beyond the apposed surfaces rests upon abundantly vascular tissue. Outside this, again, is an outer fibrous layer, which here and there becomes more condensed and reinforced to form the ligaments. Upon the apposed surfaces the synovial endothelium is more flattened and rests almost immediately upon the dense thin layer of cartilage covering so much of the heads of the bones as are liable to move one upon the other. At the junction of the synovial membrane covering the joint and the outer, saccular prolongation, the membrane is apt to be developed into a series of small papillate processes, the synovial fringes. The synovial fluid is not a simple serous fluid, but contains mucin and albumin so as to have a somewhat slimy character appropriate for a lubricating fluid.

Abnormalities.—Undue laxity of the joints, brought about by looseness of the ligaments, and favoring easy dislocation, is occasionally met. The condition is generally multiple, affecting several joints. More

serious conditions are those due to imperfect development of the bones entering into the formation of the joint. This is seen more especially in connection with the hip-joint, where the head of the femur is imperfectly developed and coincidently the acetabulum does not become adequately hollowed out, so that there is no proper seizure of the head within the acetabular cavity, and in the upright posture, the head of the femur is forced upward over the wing of the ilium (**congenital dislocation of the hip**). A similar looseness and imperfect formation may affect the knee and other joints, inducing **subluxation**.

Circulatory Disturbances.—These are inconsiderable; thus anasarca is not accompanied by any excessive accumulation of fluid in the synovial cavities. Through trauma there may be **hemorrhage** into the joint and the resultant coagulation may lead to the development of one form of foreign body therein, often subsequently absorbed.

Inflammation.—A notable feature of inflammation of the joint (**arthritis**) is the sympathetic inflammation, exudation and swelling of the soft tissues around it. Nor is the extent of this swelling by any means a sure indication of the severity of an arthritis; an acute "strain" of the ligaments may be rapidly followed by intense surrounding swelling, although the actual injury to the joint is of simple nature, slight and localized.

Following contusions there is in addition to this surrounding swelling a rapid increase in the serous contents of the joint cavity so that in the knee, for example, the patella is "floated" or pressed away from the underlying bony surfaces. This **serous arthritis** is secondary to hyperemia and is the simplest form of exudate, with few leukocytes. It tends to undergo absorption but occasionally the inflammation becomes chronic with thickening of the synovial membrane, vascularization and proliferation of its surface layer. The forms of trauma setting up serous arthritis may be various, either a contusion, a "strain," a loose cartilage or the sudden entrance of the same or other loose body in the joint between the joint surfaces. With more acute irritation there develops the condition of **serofibrinous arthritis**; the fluid in these cases is no longer clear but turbid, and if the joint be opened there is intense hyperemia of the synovial membrane with slight fibrinous deposits in the recesses of the synovial sac. The turbidity is due to an increased migration of leukocytes into the fluid. More severe and destructive inflammation, due to the presence of pyogenic organisms, results in **suppurative arthritis**. With this the synovial membrane becomes eroded and more particularly there is apt to be a degeneration and erosion of the joint cartilages, following upon which the process may extend into the bone setting up an **osteo-arthritis**. Where these erosions take place there is a process of healing if the joint be kept immobile: adhesions may occur between the apposed joint surfaces and with organization and formation of dense connective tissue across the joint cavity the movement of the joint is almost entirely arrested. Where the

destruction has been very extensive there may indeed be developed a universal adhesion between the two surfaces and in the process of time, bony **ankylosis** be set up, true bone replacing the fibrous tissue. It may be noted that where serous and serofibrinous inflammations are long continued, with voluntary immobilization of the joint by the sufferer, although the joint surfaces are not involved, nevertheless the thickening of the synovial membrane, the fibrosis, and shortening of the ligaments may also lead to rigidity and to a condition of **false ankylosis.**

Possibly our clinical distinctions of the various forms of acute arthritis are at the present day inadequate. We have already dealt with what clinically we term **acute rheumatism** or **rheumatic fever.** This term is employed to designate a condition of obvious infection with high fever, redness, pain and swelling of one or many joints, presenting itself with considerable suddenness. Wherever this occurs, we believe that we deal with a bacteriemia. Arthritis may show itself as a complication of known infections, *e. g.*, generalized bacteriemia, gonorrhœa, scarlet fever, etc., at other times may follow acute tonsillitis or trauma, at others may have no recognizable source. Bacteriological examination may yield growth of various organisms or may be negative. The transitory nature of the polyarthritis in scarlet fever, and again after the administration of sera, suggests that not only bacteria but toxins are capable of setting up joint irritation. In these last cases, we probably deal with a serous arthritis, but as regards the conditions set up by the actual bacteria, it is evident that according to their virulence we may have a serous, a serofibrinous, or a suppurative arthritis.

This purulent arthritis is characterized by two series of events; on the one hand, it is apt to originate by extension of the suppurative process either from the surrounding soft tissues or from the bone, or again from traumatic entrance of infection, and, on the other hand, is apt to extend beyond the limits of the joint either, as above noted into the bone itself or into the surrounding soft tissues, or both.

There is a disease which it is usual to include among the chronic joint diseases, but which we are convinced should be more properly regarded as an acute disease, as a recurrent acute or subacute arthritis; we refer to **arthritis deformans.** Here over long years the patient is subjected to a succession of slightly febrile attacks with accompanying exacerbations of pain and swelling of the joints and the periarticular tissues. With this the joints show progressively increasing deformity and progressive inflammatory thickening of the surrounding soft parts. The histories given indicate that there has been primarily a pure arthritis but with successive inflammations the process extends into the apposed ends of the bones leading to a rarefaction of apposed surfaces with flattening, compression even up to the stage of eburnation, and distortion, while simultaneously the process extending to the periosteum in the neighborhood induces there a proliferative overgrowth, often with

"guttering" and subsequent locking of the joint, the whole accompanied by great deformity. We have seen such a joint after many years showing purulent contents, though this is probably an unusual event. Worthy of note is the involvement of the spine in this disease (**spondylitis deformans**). Here the inflammation spreads to the periosteum and ligaments of the vertebræ, and with the new bony growth that results, there is developed a complete superficial ankylosis between individual vertebræ, with or without accompanying distortion and curvature. The bony overgrowth is apt to encroach upon the small foramina through which the nerves course, and severe continuous pain may thus be caused.

Chronic Rheumatism.—Apart from the specific forms presently to be considered, there is a certain number of cases which appear to be the result of a latent or continued process such as is seen in acute rheumatism; these are characterized by great thickening and shortening of the synovial membrane, the fibrosis extending to and involving the surrounding ligaments; with this the cartilage of the joints undergoes degeneration and at times replacement by fibrous tissue and either there may be adhesions developed or with atrophy of the heads of the bones the joints may undergo subluxation. Unlike arthritis deformans there is here little or no periosteal activity and new bone formation. It has been called **arthritis pauperum**.

Tuberculosis.—Two joints stand out as peculiarly liable to be the seat of tuberculous affection, the hip ("**hip-joint disease**") and the knee (formerly called "**white swelling**"). Less frequently, but still often, the ankle, wrist, and elbow are affected. As to the mode of origin of the disease, this may be said, that the joint disease rarely accompanies generalized tuberculosis; more frequently it is present for months or years before the infection shows signs of generalization. As to the mode of development two main forms are recognized: (1) that in which the bone in the immediate neighborhood has been first involved, and by caseation and necrosis the joint surface has become invaded, so that the joint as a whole becomes infected; this appears to be the more common; and (2) where the synovial infection is primary, tubercles forming in the inner layer. In either of these cases it is usual to speak of the disease as primary in the one part or the other, but it must be remembered that according to general belief the actually *primary* focus is in the lungs or elsewhere, even although this focus may in the meantime undergo arrest while the process advances in the neighborhood of the joint. The synovial form occasionally is of acute development inducing an abundant serofibrinous exudation; more frequently this, like that originating from the bone, has a chronic course, viz., with the formation of tubercles on the synovial membrane and surrounding inflammation; that membrane exhibits proliferation and fungoid overgrowth, becomes notably thickened, and not only is the outer layer involved but the surrounding soft tissues become infiltrated with the tubercular growth and swollen. With caseation and breaking down of the infected tissue

there may be final fistula formation. Coincidently with these processes, the bone if not primarily the seat of infection, becomes secondarily involved in a rarefying tuberculous osteitis with necrosis (**caries**). Here, as in arthritis deformans, there may be a coincident superficial formation of bone by the periosteum in the neighborhood of the inflamed joint in the form of osteophytes.

Syphilis.—In the congenital disease an exudative form has been recorded with disintegration of the cartilages and fibrosis and thickening of the capsule. In acquired syphilis, there may be an acute serous or serofibrinous arthritis in the eruptive stage, or later there may be small-celled infiltration or gummatous formation in the synovial membranes, either primary or secondary to a syphilitic osteitis or periosteitis.

Regressive Changes.—Atrophy.—The most important degenerations occur in connection with the joint cartilages. Here we may encounter either a fatty degeneration or a necrescent state of the cartilage cells and with this a coincident dissolution of the matrix. This is often very characteristic in old age; the matrix becomes more mucoid and the fibrillation becomes prominent. The general result is that under pressure the cartilage shows a tendency to ulceration with secondary sclerosis and eburnation of the exposed underlying bone. In other areas the degeneration may be followed by some proliferation of the remaining cartilage cells, and calcification with opaque whitening of these areas may eventually show itself.

The remarkable condition of **ochronosis** is characterized by a deep brown or blackish coloration of the cartilage. It is very rare and little definite is known about its causation. It must be remembered that cartilage has an affinity for iron and also for blood pigment and that thus if there be hemorrhages in the neighborhood of the joint, the cartilage may become the seat of a hematoidin pigmentation.

Gout.—Another infiltration that is very characteristic, is that seen in the gouty joint, especially the metatarso-phalangeal joint of the great toe. Here the cartilages either generally or in patches may take on a chalky white opacity, which is found, upon microscopic examination, to be due to a dense infiltration of the matrix with fine acicular crystals of sodium biurate (see p. 102). The same deposit may be seen in the synovial membrane and its underlying soft tissues and ligaments. In the surrounding tissues, these deposits may occur as **tophi** or small localized nodules. In general, if the crystals be dissolved out, it is found that the cartilage is necrosed, whether as a preceding or a sequent process is yet debated.

Neuropathic Atrophy.—In the course of some cases of locomotor ataxia and syringomyelia it may happen that with complete absence of pain an individual joint, such as the knee-joint, may undergo a relatively rapid, non-inflammatory effusion of fluid into the joint cavity with coincident atrophy of synovial membrane, cartilages and bone, whereby in a very short period there is developed a greatly disorganized joint cavity allowing a flail-like motion of the limb in all directions. This is

known as a "Charcot's joint." We are still unable to ascribe any cause to this, but conclude vaguely that here we deal with atrophic disorder, due to the destruction of the sensory portion of the reflex arc. This does not satisfactorily explain why only a single joint is involved. It may be recalled that a singular rapid atrophy of bone is seen in some cases of anesthetic leprosy.

Foreign Bodies.—Foreign bodies in joints may be of more than one order. The **corpora oryzoidea**, often found in the tuberculous joint, are little, translucent rice-grain-like bodies, sometimes concentric, formed of hyaline material with occasional indications of cells. These are regarded either as masses of hyaline fibrin or as dissociated portions of necrosed granulation tissue. As already noted, fibrinous masses from old blood clots may form soft foreign bodies; pieces of the synovial fringes may be nipped off and become free in the joint cavity. In addition there may be firmer loose bodies formed of snared-off projections of the synovial membrane which have previously undergone cartilaginous or bony metaplasia.

Progressive Changes.—Metaplasia, as already noted, is not infrequent in connection with the joint cartilage. This may become converted from the hyaline to the fibrous form and again may become converted into simple connective tissue, which, in its turn, may undergo ossification. So, on the other hand, the synovial fringes may either become so fatty as to be lipomatoid or, on the other hand, may show cartilaginous change, while in arthritis deformans bony plates may form in the synovial membrane.

Tumors.—The synovial fringes may show a diffuse **fibromatous** or **lipomatous** change. The so-called **lipoma arborescens** originating in these fringes has been recorded in several cases of tuberculous arthritis and arthritis deformans. **Sarcoma** of the synovial membrane is very rare.

THE SKIN

Since most of the diseases that affect the skin produce effects that are superficial and visible, it is obvious that the pathological effects and the clinical signs of these diseases will be largely identical; we will therefore deal with all these in the most brief way. The circulatory activity in the skin, the secretion and excretion performed by it, its function as a sense organ—all these, as well as its exposed situation—render it the seat of changes more active and more numerous than might be at first thought.

Abnormalities.—The skin may be locally unpigmented in areas that are irregular in size and shape, and pure white (**leukoderma**). A general absence of pigment in the skin and other pigment-containing areas constitutes **albinism**. Excess of pigment is found in **pigmented moles,** which are usually brown or brown-black. An interesting congenital state is **ichthyosis** in which there is great keratinization following upon hypertrophy of the skin; large fissures appear in the surface, and the

skin becomes like that of a fish or an alligator. There may be much atrophy of the active layers underlying this superficial hypertrophy.

The nails may be absent or hypertrophied, and the hair absent, sparse, or abundant. **Hypertrichosis, hirsuties** or **hairiness** may be general, the entire surface except the palms and soles being affected, a condition which is responsible for the "dog-faced-man" of museums. Localized hypertrichosis is seen on moles and over occult spina bifida.

Circulatory Disturbances.—**Anemia** is manifested by the skin in states of general bodily anemia, and locally and temporarily from cold, pressure, and emotion or other purely nervous influences; the facial pallor in a fainting attack will appeal to all as a familiar example. **Acute hyperemia** consists of a temporary dilatation of the superficial capillaries, the skin becoming pink or red; this may be the response to different kinds of stimuli, such as heat, cold, emotion, *e. g.*, blushing, friction, a chemical irritant or may be the early stage of inflammation. **Passive hyperemia** is seen in conditions of general venous congestion, as in suffocative attacks or severe fits of coughing, in overfilling of the heart, and impeded respiration from any cause. The skin then assumes a dusky tint, and the mucous membranes may be bluish or lead colored (**cyanosis, lividity**). In cases of severe long-continued passive hyperemia, **œdema** or **anasarca** may supervene, with the result that the tissue becomes smooth, tense, and shiny, the skin and the underlying loose tissue being "waterlogged."

Dermographia is seen in great irritability of the vasomotor nerves, so that if the finger nail be drawn across the skin there is quickly produced a red line corresponding to the area touched. This may be raised from the surface by a local and temporary œdema.

Hemorrhage into the skin may occur from trauma, from extreme infections in which petechiæ are seen, or from the "hemorrhagic" diseases, especially scurvy. In the last-named the extent of the hemorrhagic patch may be considerable, and in marked contrast to the extent may be the superficiality on section. The various tints assumed by the skin after hemorrhage, due to chemical changes in the pigment, are familiar. The occurrence of hemorrhage in the skin is usually designated by the term **purpura** (see p. 438), and is due to a more or less rapid degeneration of capillary walls. Finally in circulatory disturbances of the skin, it must be remembered that many states appearing *through* the skin do not actually concern the skin at all, and are connected with underlying tissues.

Inflammation.—There are numerous causes, direct and indirect, by which the skin can become inflamed; of the former, wounds of all sorts, friction, chemical irritants, heat and cold, bacterial and other parasites, are the most important; the latter comprise noxious agents carried to the skin by the blood, as well as those disturbances of nutrition and of nerve connection which, while perhaps not effective of themselves, are yet strongly predisposing forces.

While the main feature of inflammation of the skin is the exudation,

nevertheless it appears in a great variety of forms, the macule, the papule, the vesicle, the pustule, the bulla, the node, the wheal, all of which are aptly called primary efflorescences to distinguish them from crusts, scabs, erosions, ulcers, furrows, and scales which are the secondary results of such efflorescence. To apply the term dermatitis to all such appearances would be misleading because that term has become gradually restricted to particular forms of inflammation of the skin. Any attempt at classification made here will be elementary, merely to subdivide a too bulky list of diseased conditions.

I. **Inflammations of the skin due to systemic disturbance.**

Measles.—In measles the skin shows round, discrete, flat or slightly raised red or bluish-red spots, 2 to 10 mm. in diameter, fading to yellow on pressure, which under exceptional circumstances may be hemorrhagic or confluent. The exciting organism is not known, and the skin rash is distinctive only in connection with the systemic signs and symptoms.

Scarlet Fever.—In scarlet fever (scarlatina) there is an eruption of pin-head-sized or smaller red areas (punctæ), with which is usually combined a diffuse reddening of the otherwise unaltered skin, both disappearing on pressure; the scarlet tint of the skin is characteristic.

Erythema.—A great many forms of hyperemia of the skin are grouped under the term erythema—often called **erythema multiforme** because of the impossibility of distinguishing these from one another in their morphology or etiology. There is nothing distinctive about the red areas of the skin, which fade under pressure; they may become changed by hemorrhage, or by the formation of papules, vesicles, or other modifications. We have to recognize a large number of agents which can cause erythema, such as the local exhibition of heat, cold, chemicals or mechanical irritants; the invasion of the body by some toxin, as after the ingestion of certain drugs, quinine, turpentine, salicylates, mercury, or of certain foods (this often an idiosyncrasy), shell fish, fish, strawberries, etc.; as a result of certain infections, as seen in the "roseola" of typhoid fever, the bacterial agent being present in the lesion; as an accompaniment of sapremia in many different infections, and after surgical operations. Finally, many cases of erythema occur in which no cause can be assigned, and, accompanied as these often are by gastro-intestinal disturbance, we suppose that toxins elaborated in the alimentary canal or elsewhere possess the power of causing this manifestation.

Erythema of a diffuse type or localized and nodular (nodosum) may, of course, occur in specific infections, as in syphilis, rheumatism, and other states. In designating such, we are accustomed to lay more stress upon the disease that we know to be the cause than upon the non-distinctive erythema—thus in speaking of **erythema syphiliticum** we mentally underline the latter rather than the former word.

Urticaria.—Here we deal with not only a hyperemia but also with an œdema of the tissues, showing itself as slightly raised, pink or yellowish-red areas (wheals) of any size and shape, with a slight surrounding zone of hyperemia, which appear quickly and may as quickly disappear.

Familiar to most people as the homely "hives," they may be caused by nettles or a like external irritant, by the injection of the various sera, and by any of the drugs or foods or toxins mentioned above; they have some obscure relation to the nervous system, for they arise in some persons as a result of a finger-nail drawn across the skin, and in others without apparent irritation as the condition of angioneurotic œdema. Referring to rashes which are the result of foods, urticaria is a more common phenomenon than is erythema.

II. Inflammation of the Skin from Heat and Cold.

Burning.—The dermatitis set up by heat varies according to the degree of the heat and the length of time in which it acts; burns are actually classified by us in every-day hospital life in a similar way. In the lightest grade of burn, such as sometimes follows bright sunlight, there is active, followed by passive hyperemia, and a moderate amount of swelling, followed later by a brownish color of the skin. More severe degrees are attended by lifting of the damaged epithelium by the exudate—the bulla or blister. The covering of the bulla may degenerate, or the contents become infected; the corium is almost certain to suffer in such a case, but unless severely infected, scarring is not likely to ensue. More severe degrees of burning are followed by destruction of any or all of the parts concerned, leading to gangrene or to dry charring of the tissues. Here may be mentioned the parallel cases of burning by x-rays and other forms of radiant heat; the burn is not at once evident; but degeneration and cell death may follow, with the production of ulcers which are hard to heal, and whose healing processes seem to readily pass on to new growth.

Freezing.—The injury in slight cases of frostbite is perhaps as much due to the overaction of repair as to the severity of the original lesion; in a slight frostbite, as soon as reaction has occurred, the picture is the same as in a slight burn; in severer cases blebs occur, and in the severest, gangrene, there being evident various degrees of degeneration, or even necrosis, as a result of the freezing process.

III. Miliaria, Herpes, Eczema, etc.

Miliaria.—Miliaria is an eruption of tiny droplet-like areas of epithelium lifted by secretion, which seems to occur in connection especially with the mouths of sweat glands. Its causes are obscure, but probably inflammatory.

Herpes.—This is an inflammatory disease of the skin occurring in connection with the peripheral nerve trunks (see p. 120), appearing as small papules, which quickly become vesicles, containing clear or turbid serum; with the drying-up process, crusts form, under which the epithelium is renewed. According to distribution there are many varieties; **herpes zoster** (intercostal nerves), **herpes facialis, and herpes preputialis,** are common forms.

Pemphigus.—This name groups together many diseases of various origins, which are alike in this, that there are produced on the skin vesicles, at first compartmented, but later single-chambered, attaining

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large size, sometimes that of a goose-egg. The contents, at first clear, may become either turbid from fibrin, epithelial debris and leukocytes, or purulent or hemorrhagic. The surrounding inflammation often is slight, out of proportion to the size and appearance of the bulla. Sometimes pemphigus seems to be of an acute infective nature and leads to a fatal result; it is seen in the newborn as a result of syphilis and at times seems to be dependent largely upon the nervous system for its origin.

Eczema.—This term is employed to indicate an ill-defined inflammatory disturbance showing a basis of diffuse reddening and swelling, upon which there are foci of more productive or more destructive disturbance. If these foci take the form of papules, we speak of **eczema papulosum;** a very common form is that in which small lenticular vesicles develop (**eczema vesiculosum**). These are particularly apt to rupture under irritation and lead to oozing (**eczema madidans**); where more chronic, the weeping surface is apt to give rise to the formation of scattered crusts, or the vesicles may become pustules (**eczema pustulosum**). As a result of the chronic condition, pigmentation and thickening of the skin are apt to be seen. In attempting to define eczema it may be said that a discrete eruption does not constitute an eczema; there must be an underlying inflamed basis. If there be simple inflammation without foci of further disturbance we speak of erythema; if these foci of further change occur, of eczema; if these foci develop to such an extent as to overshadow the background of diffuse inflammation, we are apt to speak of the focal disturbance and neglect the diffuse dermatitis; to speak, for example, of **impetigo, intertrigo,** etc. From the pathologist's point of view it appears as if eczema were a term used by clinicians for convenience in designating many confusing forms of dermatitis.

Impetigo.—This is an infective disease oftenest of the face and hands (frequently by transference) in which small pustules arise, with subsequent crusts. The common form is designated **impetigo contagiosa;** from the nature of the contents of the pustules one would judge that under favorable circumstances most of the cases, if not all, would prove communicable. We recall that, during our college days, an epidemic occurred in the football team, the eruption appearing in some cases behind the ear, where the skin frequently was broken by the auricle being pulled forcibly forward in the pressure of the scrimmage; after a certain match members of the opposing team developed a similar condition, similarly located, the result of head-and-head contact.

IV. **Inflammation of the Skin Characterized by Pocks.**

Variola.—As a result of hematogenous infection, a coagulation necrosis occurs in the cells of the rete Malpighii, with a cellular exudation from the vessels of the papillæ; by the action of pyococci the contents of the many-chambered pock become infected and, finally, a single-chambered pustule results, which forms a crust and ultimately may leave a scar. Of the same general order are the pocks of varicella, and of vaccinia.

V. Psoriasis, Lichen, etc.—Psoriasis is an inflammation of the skin in which an infiltration of the epidermis and corium occurs; there are punctate heaps of broad plates of dry epidermis on a background of sharply defined reddened skin that bleeds easily. The epidermal cells of the stratum corneum dry and are separated into large plates or flakes between which air finds its way, giving the characteristic silvery appearance to the scales.

Lupus erythematosus, in no way connected with true lupus, is an inflammation that shows itself as small round, raised spots with a depression in the centre; these become covered by dry, yellow scales.

Lichen is a chronic form of inflammation with papules which remain unchanged save for an increase in size; they may form scales, but not vesicles or pustules, although in **lichen scrofulosum** there may exceptionally be tiny pustules on the summits of the papules. The mouth of the hair follicle is the part affected, a perifollicular inflammation and hyperkeratosis resulting.

VI. Erysipelas and Other Inflammations of Known Bacterial Origin.

Erysipelas.—This is an infection of the skin, sometimes by way of an unrecognized lesion, sometimes by increase of virulence of the cocci in hair follicles, which may be accompanied by great or by slight systemic disturbance; often the latter is out of proportion to the amount of skin involvement. Formerly considered dangerously infectious, the disease is now placed on a par, in this regard, with other forms of sepsis, viz., danger exists chiefly for those afflicted by wounds or great bodily weakness. The lymph spaces of the connective tissue lodge the bacteria, usually streptococci, and there is marked hyperemia, cellular and serous exudate, which progresses with the existence externally of a well-defined line of demarcation. The skin is swollen, shiny, and red. Vesicles and pustules may form and even severe necroses may follow.

Abscess or Phlegmon.—Abscess or phlegmon does not differ greatly from the above in its mode of origin; fluid exudation and the distension of the tissues are more evident. The result of infection of the skin may be a diffuse **cellulitis** on the one hand, or a localization—abscess—on the other. By reason of concentration and bacterial activity, the abscess may attack the deeper structures, and attain considerable depth before the pressure becomes sufficient to break through the skin or before surgical intervention is secured.

Acne.—This is a small inflammatory mass originally formed in the vicinity of a hair follicle or a sebaceous gland, breaking down to form a small quantity of pus. **Acne rosacea** has a different origin; here is found, in the simplest forms, a prominence of capillaries over the surface of the cheek or nose, while in severe forms there is a marked increase in the connective tissue and the glands, which latter become closed, and a great deformity—a kind of elephantiasis of the nose—results.

Furuncle, Carbuncle, etc.—The **furuncle** is, pathologically speaking, an acne pustule upon a larger scale; and a **carbuncle**, upon a yet greater scale. In the last, by reason of the virulence of the organism, usually

in all these cases the staphylococcus, there is apt to be a widespread necrosis of tissue and a marked systemic disturbance. When the infection is not staphylococcic or streptococcic but due to the bacillus of anthrax, the lesion is designated **malignant pustule**. In **necrosis** and **gangrene** the skin is but one of the tissues involved; these have been dealt with elsewhere (p. 298).

Ulcers.—Ulcers of the skin arise in many different ways, and may follow many causes; the essential condition is a loss of tissue brought about in other than a sudden way. Normally the process of repair comes at once into action, and according to the completeness of this reaction and its speed, coupled with the quality and amount of exudate, the ulcer takes certain characters, indicated by names such as **healing**, **spreading**, **indolent**, or **phagedenic**. The tendency of new growths of the skin to ulceration is very great, by reason of their poorly-controlled blood supply and of the readiness with which interference with the circulation of the skin is produced.

VII. **Infective Granulomas.**

Tuberculosis.—**Lupus** appears as a nodular eruption, which consists of an agglomeration of miliary tubercles surrounded by an inflammatory infiltration, seen most often upon the face. The nodules may be at times hardly visible, but may be felt, and if a moderate degree of absorption occurs, the area may be ultimately scarred, but in some part of its course ulcerative destruction of some part of the surface is almost the rule. Scarring may be extensive, and there is a tendency for the disease to recur in the scar tissue. Histologically, the characters of the tuberculoma are seen amid inflammatory infiltration by leukocytes and plasma cells. Tubercle bacilli are present usually in small numbers.

The so-called **scrofuloderma** or subcutaneous tuberculosis consists of a subcuticular infection often in the neighborhood of tuberculous glands or fistulæ. The infiltration by small tuberculous masses, with subsequent infiltration of the skin itself, is seen as an apparent adhesion of the thinned layers of the skin to the underlying tissues, the whole being bluish-red with a considerable tendency to caseation and necrosis. Miliary tubercles of the skin may be seen in some cases of generalized tuberculosis, and localized tuberculous warty growths may occur on the hands as a result of a "post-mortem wound."

Syphilis.—The **chancre** is found most frequently upon the genitals but may occur in many other regions, and is usually single. After an incubation period suited to the relatively low grade of virulence of the spirochete, a sharply defined, painless, small, hard nodule is found, with a deeply lying base of firm tissue which extends outward on all sides beyond the actual nodule. Microscopically the infiltration of leukocytes and plasma cells in the perivascular regions is very marked, as is the proliferation of the fixed tissues which gives hardness to the mass. The manifestations of syphilis in the form of efflorescences on the skin are very various; the simplest is the **erythema syphiliticum** or

macular syphilide, which is seen as red, ill-defined areas of varying size tending to appear on the trunk and the flexor surfaces. They may remain for a considerable time and fade, leaving a temporary brownish pigmentation. The **papular syphilide** may show itself in the midst of an area of the erythema as well-defined brownish-red papules, on the skin dry and on moist areas such as mucous surfaces, exuberant, moist, and tending to ulceration. The **mucous plaques** of the mucosæ belong to this order, but the rapidity with which they break down leads to their appearing as flattish ulcers covered by grey debris. The papules may become infected and give origin to pustules, which again become scabbed. A combination of considerable proliferation with ulceration and scabbing gives rise to the peculiar structure of concentric crusts called **rupia**. Actual **gummas** may occur in the skin, but more often belong originally to the underlying tissue and involve the skin later. The true gummas of the skin show as flat, hard areas, like the base of a chancre, tending to ulcerate and form "punched-out" ulcers. In all these ulcerative lesions, the healing is attended by a marked degree of scarring.

Lepra (Leprosy).—This is seen in the skin as nodules of proliferated tissue containing the causative bacilli, or as yellowish-red or brown spots on the skin or mucosæ, with an inflammatory infiltration. A light scarification yields a fluid in which the characteristic bacilli are readily found (Wyatt Johnston).

Other Granulomas, Blastomycosis, Dermatomycoses, Etc.— Glanders occurs in the skin as an acute inflammation due to infection of a wound or other solution of continuity and **actinomycosis** usually as a secondary process, appearing as a chronic ulceration or as overgrowth; a lesion of like nature is **Madura foot**, of which the causative agent is *Mycetoma pedis*. Among the proliferative (and secondarily ulcerative) lesions of this nature, must be considered that formed by blastomyces, **blastomycosis**. Here a general infection of the body may occur, but more frequently a distinctly hypertrophic, sharply defined, warty, crusted growth is found. Beginning as a papule, the mass is distinctly of inflammatory type, and in the later, larger lesions minute abscesses occur in the substance; in these abscesses, as elsewhere, the yeast-like organism may be found.

Favus is due to *Achorion Schönleinii*, which succeeds in obtaining a footing in the hair follicles and setting up a low-grade inflammation with the formation of a yellowish cupped disk composed of debris which lies upon a slightly inflamed area of skin. **Ring-worm** may be caused by more than one mould, most commonly by the *Trichophyton*, and is known as **tinea**. It may affect the scalp (**T. tonsurans**), the hairless skin (**T. circinata**), the beard (**T. sycosis**, often acute by reason of coccic infection), and the covered parts of the skin (**T. versicolor**). The latter is often called **pityriasis**, and is relatively unimportant.

VIII. **Inflammations of the Skin Caused by Animal Parasites.**

The lesions caused by animal parasites are often of themselves quite

inconsiderable but are nearly always complicated by the fact that the itching set up leads to scratching and thus to secondary inflammation of various types. Most important of these parasitic lesions is **scabies**, set up by the *Acarus scabiei*, which burrows into the skin in a direction somewhat parallel to the surface, and deposits eggs in the burrow thus made. The constant and long continued irritation by scratching as well as by the insect, may lead to a general thickening and pigmentation of the skin (**vagabond's disease**). **Pediculosis** is the term applied to the lesions caused by the presence of lice of different kinds; fleas and bedbugs also cause lesions that are usually temporary. **Myiasis** is the term applied to the deposit of the eggs of sundry flies (Diptera) in the neighborhood of the various orifices of the body, and to the ensuing inflammation.

Molluscum contagiosum, referred to elsewhere (p. 375), is a blastomatoid state, inaugurated, according to some authors, by a coccidium. The **guinea-worm** (*Filaria medinensis*), and the **chigoë** are also examples of parasites that burrow in the skin.

Regressive Changes.—Atrophy.—Atrophy of the skin occurs in the old, a general process of thinning, the cutis becoming narrower, the epidermis dry, and the subcutaneous fat so greatly absorbed as to allow the skin to wrinkle. A local process of atrophy is noticeable in the skin as the so-called **lineæ albicantes**, which are whitish or silvery lines, the result of a previous distension of the skin. They are seen most commonly in the breasts, the abdomen and the thighs, and frequently follow pregnancy, though stretching of the skin from any other cause will suffice for their production.

Necrosis.—Necrosis of the skin occurs accompanying necrosis of deeper tissues in bedsores, and ulcers of other kinds, as well as in gangrene and circulatory disturbances such as Raynaud's disease.

Pigmentation.—Variations in the pigmentation of the skin are to be considered in this class. These consist of (1) loss or increase of the normal pigment of the cells of the corium, (2) the appearance of blood and bile pigments, and (3) the deposit of injected or ingested pigments. To congenital lack of pigment and to tattooing reference has been made elsewhere (see p. 292).

Vitiligo or **Leukoderma** is a localized disappearance or congenital absence of the normal pigment, seen in the dark oftener than the white races, by which irregular areas of white skin, on which the hair also is unpigmented, appear in various parts of the body. Its cause is unknown. Increase of the normal pigment is seen as a result of the action of sunlight in the **freckles** of childhood, as also in **pigmented nævi** and **warts**, in **chloasma**, obscurely connected with the genital functions, as in pregnancy, in **Addison's disease**, in "**bronze-diabetes**," after **sunburn**, after the action of physical **counterirritants**, in **hemochromatosis**, and in **jaundice**. Most, if not all, of these have been referred to elsewhere, as has the general subject of pigmentation (see p. 288). **Xanthelasma** is an ill-understood yellowish pigmentation most frequently on the eyelid.

Progressive Changes.—We have already touched upon certain conditions characterized by marked hyperplasia of the epidermis; a local hyperplasia may also be acquired as the result of chronic irritation in the case of the familiar **callus** on the palm or sole, and the **corn.** Here as the result of recurrent slight irritation there develops a thickening, an increased development of layers of keratinized epithelium. Such may be local, as in the above-mentioned cases, or may be more generalized, as in the marked thickening that occurs involving the entire sole of those accustomed to walk barefoot. A condition that must possibly be regarded as of congenital origin is the development of **cutaneous horns**, which in some cases have been reported as attaining extraordinary size, a foot or more in length. Cases of bilateral occurrence have been reported, chiefly from France. The horn is generally solitary and exhibits a base showing active growth of the deeper layers of the epidermis and overlying this is a succession of closely packed adherent layers of keratinized cells. Diffuse local thickening of the skin may further result from chronic inflammation, *e. g.*, eczema, syphilitic lesions, etc. **Warts or verrucæ** are localized hyperplasias of the epidermis, and when of large size show a coincident overgrowth of the underlying cutis, presenting a definite stalk, and sometimes becoming definitely papillomatous. The remarkable point regarding them is that after being present for years they may spontaneously undergo atrophy and disappear. There is some indication that they are of infective origin, it having been observed that they may be conveyed by contact.

A condition or group of conditions in which apparently the primary disturbance involves the dermis and subdermal tissues with secondary epidermal hyperplasia is seen in **elephantiasis.** As already indicated there are several forms of this; one group is congenital, and is comparable with macroglossia and macrocheilia. The most common form is encountered in tropical regions and is filarial in origin (**elephantiasis arabum**). Other causes, as lymphatic obstruction, lead to very similar appearances; such are obliteration of the main lymph channels of an extremity through new growth or chronic fibroid lymphadenitis or lymphangitis; while lastly, syphilitic and other chronic inflammations of the skin by causing a chronic œdema, favor the setting-up of mild orders of this condition. In all these states, it appears that we deal with a relative or actual lymph stasis, leading in the first place to enlargement of the part, and secondarily to a diffuse connective tissue hyperplasia. Due to the distension, of moderate grade, of the underlying tissues, the epidermis tends to hypertrophy, forming itself into folds and sometimes more warty and nodular overgrowths. The condition most frequently presents itself in one or both of the lower extremities or in the scrotum, the latter sometimes attaining so colossal a size as to extend below the knees.

A milder type of thickening of the skin with primary involvement of the dermis may affect considerable areas of the limbs or trunk and

is seen in the group of conditions known as **scleroedema**, **scleroderma**, and **sclerema**. Of these the first manifests itself in long-continued anasarca; it is allied to the condition seen in myxoedema, there being a brawny hardness of the affected part, with, however, little change in the overlying epidermis. In **scleroderma** a similar induration, long continued, is followed by distinct hypertrophy involving not only the dermis but also the epidermis. An associated state is seen in **dermato-myositis** in which the underlying muscles become intensely hardened and rigid, and the skin above them appears as though adherent and is capable of curtailed movement. Little is known regarding the cause of either of these conditions. Neurosis has been suggested, a condition parallel to that of angioneurotic oedema. In dermatomyositis the muscle at first shows little change beyond congestion and oedema; in both the apparent primary hypertrophy is apt to be followed by atrophic changes. **Sclerema** is a congenital condition or develops in infancy, and is characterized by a diffuse thickening and induration of the cutaneous tissues without recognizable anatomical changes. German authorities have called attention to the fact that there is here a modification in the composition of the fat, in the direction of increased percentage of the less soluble palmitin and stearin fats whereby, in place of being fluid, the fat within the fat cells is solid.

Tumors and Tumor-like Growths.—We have already referred (p. 807) to the development of **cutaneous horns** which are not strictly tumors, but undischarged keratinized cells: to **cheloid** (p. 349), in which we have a striking overgrowth of the subcutaneous connective tissue secondary to irritation, but at the same time due to congenital hyperplastic tendency on the part of these tissues: to **multiple cutaneous fibromas (neurino-matosis)** (p. 365), due to overgrowth primarily of cells of the sheath of Schwann around filaments of the cutaneous nerves: to diffuse **lipoma-tosis**, or blastomatoid hyperplasia of the subcutaneous fat: to the allied condition of **adipose dolorosa** and also to **xanthoma** (p. 351). There remain certain overgrowths which deserve more particular notice.

True **fibroma** may be present, most often in the form of solitary tumors which may attain considerable size and may be either hard or soft. **Myxoma, chondroma,** and **osteoma** are rare. We have encountered a multiple cutaneous formation of small chondromatous plaques in the skin of the legs, evidently metaplastic. The skin is, however, a favorite seat for the development of **lipomas**, more especially in the shoulder region. These solitary lipomas have a lobulated structure and may attain considerable size. Several cases of multiple small **myomas** are on record, and some of solitary myomas, of small size, originating evi-dently from the arrectores pilorum, and from the muscles of the sweat glands.

Under the heading of **naevi** (or birthmarks) and **moles** are to be grouped a number of different conditions. The hairy mole is a patch of normal skin giving origin to large, coarse hairs in a region normally hairless. Frequently associated with this there is marked pigmentation and

some hypertrophy of the skin. A section through such a mole shows frequently a more vascular condition than normal, with, in addition, a pronounced collection of chromatophores or pigment cells around the vessels. The nevus is of larger size and comprises a variety of conditions, from the soft, warty masses, showing abundant cells, to states of enormous and widespread cavernous dilatation of the superficial vessels, which may involve the whole of one side of the face, or, as we have seen, the whole head, or, again, a large portion of the trunk. The smaller, cellular forms, like certain moles, show masses of somewhat cubical or polygonal cells surrounding somewhat enlarged vessels.

Fig. 380

Section from a case of hemangioma simplex, exhibiting progressive enlargement and extension. (Borrmann.)

In the larger, the dilated vessels predominate and cause a striking bluish or reddish coloration of the affected area ("**strawberry mark**"). The condition is most often what has been termed **cavernoma,** or cavernous angioma, but occasionally we meet with not merely this dilated condition but a true blastomatous proliferating **angioma** with progressive growth into the surrounding tissue. So, also, at times we encounter conditions of **lymphangiectasis** which may weep, and true cutaneous **lymphangiomas,** or **lymphangio-endotheliomas.** Any of the above connective-tissue tumors may give rise to **sarcoma** or to sarcomatous developments. At the same time primary sarcoma does occur, round-,

spindle-, or mixed-celled together with a remarkable form of diffuse **sarcomatosis** of the skin which may involve large areas (**mycosis fungoides**). The character of this growth, however, makes one strongly suspect that here we may deal with a spreading inflammatory condition.

A not uncommon form of malignant tumor is the **melanoma** or **chromatophoroma**. We hesitate to give this its usual name of melanotic sarcoma, inasmuch as there is still considerable discussion as to whether this be of epithelial or perithelial origin. These tumors originate usually from a pigmented nevus or mole, and in these from the large polygonal cells or chromatophores situated immediately around the vessels. We have repeatedly called attention to the abundant metastases which they are liable to set up.

Carcinoma.—The malignant epithelial tumor of the skin is naturally the **squamous-celled carcinoma** (**epithelioma**), but of this two forms are recognizable: the one, the squamous epithelioma proper, such as is seen on the lip, scrotum, or penis, is characterized by large, moderately coarse, finger-like processes dipping down into the underlying tissues, presenting well-marked epithelial pearls, and with its deep infiltrative powers, manifesting a marked tendency to develop metastases in the neighboring lymph nodes. This may originate either from the cutis proper or from the hair follicles or sebaceous glands and shows a marked tendency toward ulceration. . The other form, the **rodent ulcer**, presents itself most commonly on the upper part of the face, where it is characterized by slow growth, extending sometimes over years, shallow and dry ulceration, fibrosis and cicatrization in certain parts with slow extension and eating away of the superficial tissues, and often a superficial wrinkling by reason of the contraction of the fibrous tissue. A remarkable fact is that only late in its course, when there has been much erosion, does this show deep infiltration and the formation of metastases. Microscopically the cell columns are small, irregular, with absence of epithelial pearls. The simpler type of cell seen in this form with its departure from the typical prickle-celled type, led Krompecher to include this among the basal-celled carcinomas, on the unfounded supposition that it originates from the deeper Malpighian layer rather than from the fully formed epithelial cells. There is no evidence for this assumption, but by analogy we must say that the tumor is composed of cells that have undergone a greater anaplasia and have lost the capacity to develop the more differentiated cell. The observations of Wolbach upon the closely allied x-ray cancer of the extremities and other regions, affords, it seems to us, a possible explanation for the absence of metastases in this form, viz., in the latter form it is evident that a fibrosis with condensation of the dermis precedes the cancerous change in the epithelium, and in this way, by the destiny of the underlying connective tissue, affords a barrier against the easy penetration of the cells into the deeper lymphatics.

Secondary carcinoma of the skin is not very common; it is seen most often in connection with mammary cancer, one form of which shows a

peculiar tendency to spread along the cutaneous lymphatics, giving rise to the so-called "cancer en cuirasse."

Cysts.—**Retention cysts** may show themselves in connection with the sebaceous glands, often secondary to a condition of **seborrhœa** or hypersecretion, resulting in the production of **wens** on the scalp or **sebaceous cysts** elsewhere. Retention cysts may also affect the sudoriparous glands, again following hypersecretion, resulting in **miliaria**, minute, clear tense vesicles immediately underneath the upper layers of the skin. In this connection we may mention the allied condition of **comedones** ("blackheads"), a condition due to the blocking of the ducts of sebaceous glands by plugs of sebum and desquamated cells. They are most commonly seen upon the nose and chin. Yet another form of cyst deserves mention, the **implantation** cyst, brought about by the traumatic forcing of cells from the deeper epidermal layers into the dermis (see p. 411), and the rarer true **cutaneous dermoid** due to an embryonic inclusion of epithelial tissues in the deeper layers during the process of closure of various fissures.

THE HAIR

Certain diseased states of the hair call for notice. There may be excessive production of hair (**hypertrichosis**) either over the greater part of the body or in particular regions, notably over the site of an occult spina bifida or, in the female, on the chin and lips. Absence of hair from regions where normally it should exist is spoken of as **alopecia.** This may be congenital, and then either universal, or as on the mons, in the axillæ, and on the face, associated with a lack of development of the secondary sexual characters; or a senile change, or premature, supposedly a trophoneurosis. Apart from this, it may be a manifestation of a distinctly local trophoneurosis, round or oval areas of the scalp being affected (**alopecia areata**). Similar local loss of hair may follow the growth of sundry moulds, *e. g., trichophyton*, or in localized inflammations or after infective fevers. Nutritional changes in the hair are little understood; premature whitening (**canities**) may be found due to arrested development of pigment, without of necessity any other sign of defective growth, and may also follow severe nervous shock, or continued nervous irritation as in migraine and neuralgia; sometimes local patches of canities constitute a family trait. Other disturbances due to defective nutrition are splitting of the hair, clubbing of the end of the hair, uneven caliber of the hair, or beading. In certain of the above-mentioned parasitic diseases, the defective nutrition of the hair is manifest in its brittleness.

THE NAILS

Abnormalities of the nails are rare. **Hemorrhages** may occur in the bed of the nail in cases of malnutrition combined with sudden changes of temperature. **Inflammation** may attack the tissues at the root of the nail (**onychia**) or at the edges (**paronychia**) leading to suppuration and sometimes exfoliation. With paronychia the relation of nail and soft part may be altered so that the nail penetrates the deeper tissues (**ingrowing toe-nail**), while flecks due to the presence of air between the layers of the nail may appear in the body of the nail (**leukopathia**), or a transverse furrow may mark on the surface the date of a past acute illness, both of these being evidences of temporary malnutrition. The nails may grow to an enormous extent (**onychogryphosis**) with great deformity in shape, in this comparable to the development of cutaneous horns. Parasitic diseases of the skin (**favus, ring-worm**) may affect the nails, and the mycelial threads may actually penetrate and grow within the nail substance.

APPENDIX

MONSTROSITIES AND ABNORMALITIES

The terms denote grave anatomical departures from the normal, either general or local, and the term monstrosity is applied to the more pronounced of these. Departures from the anatomical normal consist of variations either in the direction of excess or of defect, or of altered relative position of parts.

Abnormalities of Excess.—This may show itself in excess of the individual or in numerical excess.

Individual excess may be (a) universal, i. e., **giantism**; (b) lateral, i. e., where one side is larger than the other, as if there had been unequal division when the first two blastomeres were formed; or (c) local, where one member or organ is markedly larger than the standard set by the rest of the body. Giantism applies to those human individuals who are more than 200 cm. high. that is, 6 feet 6½ inches, a height that is usually due to the great length of the legs. Giants usually spring from families in which the individuals are of medium height. Lateral giantism cannot well be extreme. Local giantism may either be true or may be acquired by disturbed nutrition, in which latter case it is often of congenital origin. Thus, localized **elephantiasis** of a limb or **macroglossia** or **macrodactyly** (where a finger is abnormally large) may be due to obstruction of the lymph channels, and consequent overgrowth of connective tissues. Where, however, there is not only macrodactyly but duplication of fingers or a tendency thereto, it is safe to assume that there has been a redundancy of vegetative matter at the growing point. **Hypertrichosis** (hairiness) and **lipomatosis** (general obesity) are to be explained by a combination of inheritance and metabolic modifications; precocity in the development of the muscular and generative systems appears also to be associated with aberrations in development of the ductless glands.

Numerical excess includes a wide range of abnormalities from multiple births to partial duplication of a phalanx.

Twins.—Twins may be **dichorial** (heteroöphal) or **monochorial** (mono-oöphal). In the former, each child has its own membranes and placenta, although the two placentas may ultimately fuse. The children may or may not be identical in sex; they may or may not closely resemble one another; in fact, they obviously arise from two separate ova fertilized at the same period. Should the dichorial twins be of the same

sex, and very much alike in characteristics, it may be that two ova from the same follicle have been fertilized, for multiple ova in a follicle do occur; there is even one other possibility, that a single ovum after fertilization has divided into two, and that the two halves become separately implanted in the uterus. **Superfœtation**, in which the embryos are of different ages, obviously can arise only from ova discharged and fertilized at different periods.

Monochorial twins are rarer than dichorial. They have the same chorion, the same placenta, are of the same sex, and if equally developed, much alike. As the chorion is the outer wall of the ovum, it is evident that here the same ovum has given rise to two individuals. Such twins may even have identical abnormalities, such as spina bifida or hypospadias or right-sided hydrocele. Experiment upon invertebrates and even upon the lower vertebrates has demonstrated the possibility of one ovum giving rise to two individuals, and the eggs in development may even be shaken apart, when dwarfed individuals arise from the fractions of the original individual. It is possible, therefore, that monochorial twins may originate in one of the following three ways: (1) At times an ovum is seen to possess two nuclei: each may be fertilized by a separate spermatozoön (unlikely, because it is observed that the entry of one sperm cell into the ovum causes such change in the outer egg membrane that entry of others is prevented). (2) A fertilized ovum may break in two at a very early stage, as for example, when it is two-celled, or (3) a cleavage of the germinal area at a comparatively late period may give rise to two primitive streaks upon the one germinal area.

Unequal Twins.—This covers a number of cases in which a common feature is that one of the twins is normally formed; the other may be a lump of flesh, with smaller warty projections on it (not unlike a potato with small supernumerary tubers upon it), whose only claim to recognition is that the umbilical cord is attached to it; this is the **fœtus amorphus.** Sometimes there is a fair indication of the lower limbs but no head (**fœtus acephalus**), or the fœtus may consist of little more than the cherub-like head (**fœtus acormus**); the absence of a heart in many of these classes leads to their being called acardiac in addition to the other distinctive names.   In some cases, like fœtus acormus, the fœtus lies directly upon the placenta without the intervention of any umbilical cord.

The cause of these acardiac monstrosities is that the circulation in the fœtus concerned is a reversed one, because the stronger of the twins in time comes to be driving the blood through both; the allantoic and placental vessels become freely anastomosed, and the stronger twin drives blood progressively into more and more of the anastomosis, finally, into the weaker embryo's umbilical artery and aorta; hence, it is distributed in the branches and nourishes the tissues of the weaker embryo; it may be sufficient to nourish a part only, and the rest of the weaker embryo's frame undergoes aplasia and atrophy; the heart

of the weaker embryo by arrested action, incomplete activity, and relatively impaired nourishment fails to develop, but in its losing battle, it yet keeps as its own province the head end of the embryo, and it nourishes this so badly, that the cephalic end is more prone to be maldeveloped than the caudal end—**fœtus acardiacus anceps.**

FIG. 381
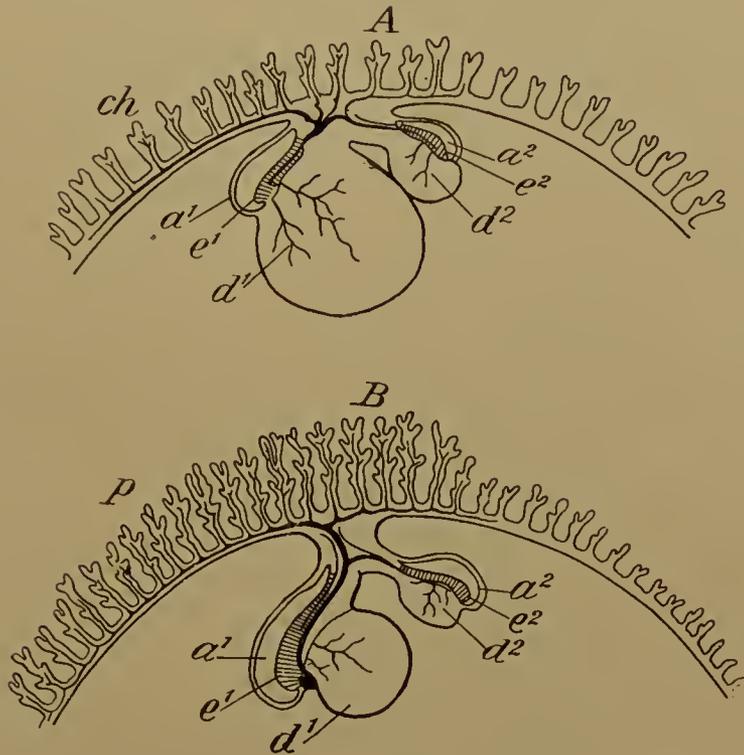
Marchand's schema of mode of development of acardiac monsters. In A the chorion ch is already developed; the yolk sac has divided into two unequal halves, d^1 and d^2, in consequence of which the one embryo e^1 receives through the yolk vessels more abundant nourishment than does the other embryo e^2. As a result, its allantoic circulation develops more actively, and the later developing allantoic artery of the smaller embryo anastomoses with it. B, later stage; the allantoic vessels of e^1 usurp the whole of the chorion, the smaller embryo gaining its blood entirely through the anastomosis of its allantoic artery with that of e^1, and this, therefore, in the reverse direction to the normal current. a^1 and a^2 indicate the amniotic sacs of the embryos.

Triplets and Other Multiple Births.—Triplets may be monochorial, or monochorial and dichorial, or even polychorial; the rules as to identity of sex and similarity of characteristics which apply to twins, apply also to triplets. Seven children at a birth is reported upon reliable (?) authority. In the cat, the monochorial development of five kittens is recorded.

Double Monsters.—There has been for many years much discussion upon the reasons for diplogenesis, and in a field where so many theories exist, we venture to put forward but one, which we term the **"growing-point"** theory. This is based upon our knowledge of the growth of a plant. If we consider that the first cell is divided into two and then four, and each of the four again into two, we find that the two poles tend to become separated, one from the other, and each pole is advanced by the cells that are built in behind it. There are in the plant, from an

early stage, two primary growing points—the superior forming the stalk and the inferior the root; the entire plant arises from one or other of these "points," and the growing point is the most advanced part of the plant; the plant increases by growth backward and not forward from the growing point, whose position is thus fixed at the apex.

The growing point does not *grow* forward but is projected forward by the intercalation of the daughter cells behind it, and the daughter cells are able to divide in a transverse way and give rise to the special tissue cells. Secondary growing points can subsequently arise from the daughter cells, but their vegetative function must be exercised now

Fig. 382

Diagram of section of the growing point of a plant, A, A, the apical cells, which continually divide, giving off backward a series of cells; B, C, which cells divide as in B^1, B^{11}, to form the cells of the vegetative or cambial layer; these cells again, as in C, C^1, and C^{11}, divide at right angles to the former plane to give origin eventually to the functional cells of the stem (or root); D, development of a secondary growing point.

in a direction more or less lateral, and no longer axial. Similarly in animals there are two "growing points"; the superior growing point is represented in the adult mammal by tissue about the situation of the pituitary body, and the inferior by tissue somewhere in the sacral region. These two points lie beyond the extremities of the chorda dorsalis, an organ whose prominence in the early embryo and whose apparent unimportance in the formed fœtus, suggest that its function may be partly the keeping of the growth axially, as a scaffolding might do, in the earliest stages. These two growing points from the very origin of the embryo are being projected apart, and the suc-

cessive daughter cells given off from these give origin to the different organs of the body, and even form secondary growing points for the limbs.

There is thus a close parallelism to be noted between the plant and the animal embryo, nor need this be unduly disturbed by the fact that symmetry in the plant is generally radial, and in the animal lateral, because there are numerous exceptions to both rules, and the lateral symmetry is the fundamental one, because cell division is binary.

But there is a fundamental difference to be observed. Whereas in the plant the primary growing points are active through the whole of existence, in the animal they cease to functionate as such when the *anlagen*[1] of the brain and of the rest of the nervous system have been developed.

If the superior and inferior growing points did not cease their activity, we would have the following state of affairs: the expansions of the neural canal which form the ventricles of the brain would have already formed themselves, and the superior growing point which is situated near the site of the pituitary body would blossom out into a mass of tissue. This may actually happen. Where is space to be found for it? There is none available, and it forces its way through the roof of the mouth to the outside as a large pediculated mass, which is called **epignathus**. These masses have at times been found to contain bone, and tissues representative of all three original layers, epi-, meso-, and hypoblast. The fact of limbs actually developing on such a mass lends additional weight to the supposition that this is but a continuance of the original superior growing point.

A precisely analogous case occurs at the hind end of the body. A mass of tissue sometimes arises behind the rectum, at the extremity of the sacrum, called **congenital sacral teratoma**. Among roses one sees a similar happening when an imperfect flower stalk and head develop from the centre of a flower.

Polar Dichotomy (Branching of the Growing Points).—In plants there is a liability for the growing points to branch, as when a fir tree, high up, divides into two or three trunks; the root of the radish may similarly fork. In some plants, a division into numerous stems is the rule. A plant may thus undergo dichotomy at any period during its growth because its growing points are always active, but an animal—a mammal, for example—only in that limited time during which the growing points are active. In the newt's egg, it has been experimentally shown that as long as the egg continues to show growing points, double monsters can be produced by partial physical division of the egg, such as may be brought about by the pressure of a hair tied around it. After the growing points cease, that is, when the medullary groove appears, this can no longer be done.

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[1] We have in our language no word to describe the matrix tissue from which organs originate, and so are forced to take this word from the German.

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Even the period, short as it is, during which dichotomy may occur, may be divided into its early and its late part. If the dichotomy occurs

FIG. 383
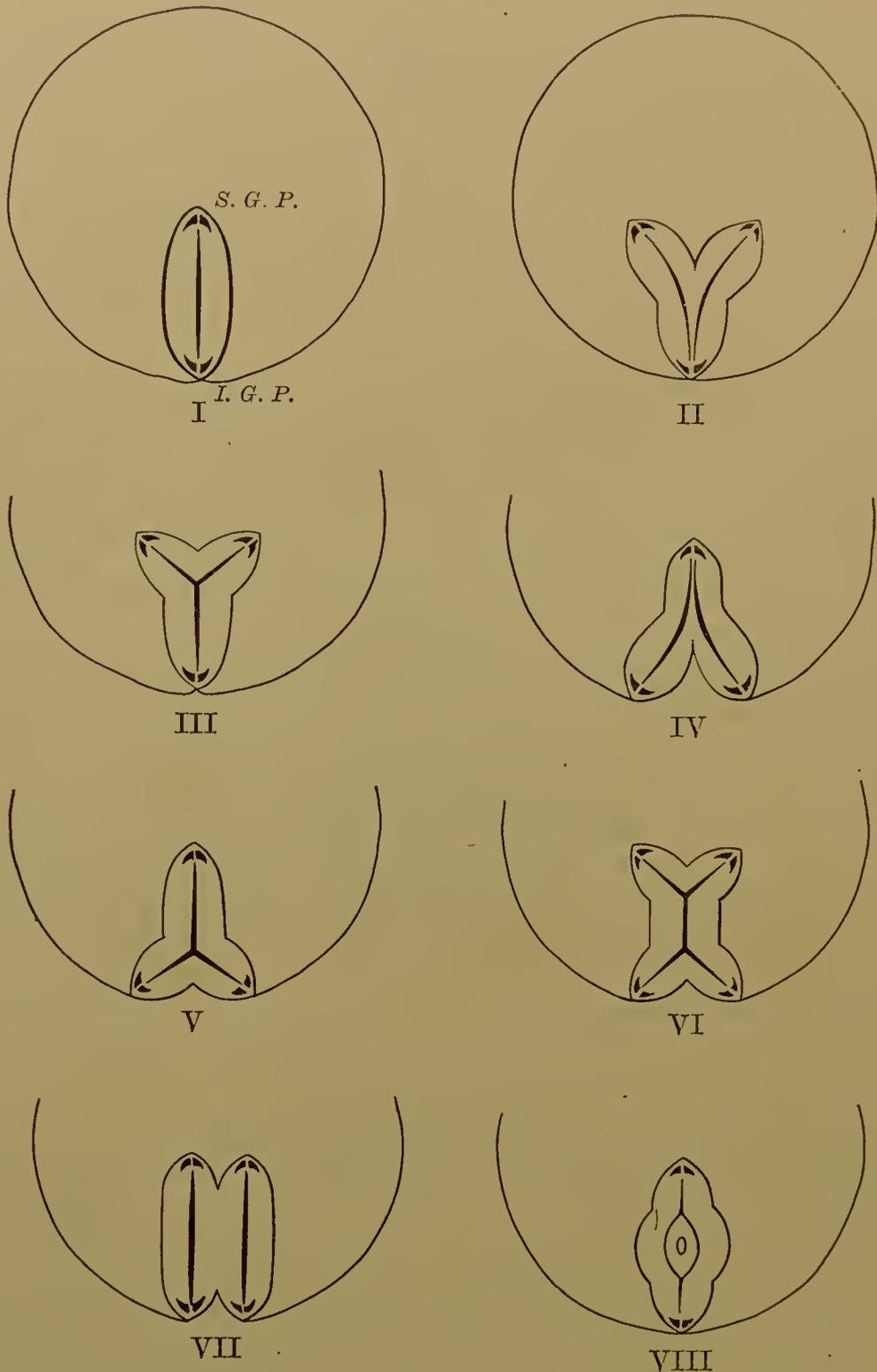
Diagram of various forms of dichotomy or cleavage: I, normal early primitive streak in germinal area with *S.G.P.*, superior, and *I.G.P.*, inferior growing point; II, result of early dichotomy of superior growing point, the separation affecting also the lateral rows of cells given off from the inferior growing point; III, late dichotomy of superior growing point, only the cells given off more recently from the two superior growing points affected; IV and V, similar results of early and late dichotomy of the inferior growing point; VI, relatively late dichotomy of both superior and inferior growing points—anakatadidymus; VII, early (complete) dichotomy involving both growing points—fused double monsters, lateral fusion; VIII, mesodidymus, the growing points remaining single, but the series of cells derived from them on either side undergoing separation.

early enough that every cell born from the superior growing point diverges from its fellow, we have a duplication of the entire animal, as far back as the cells which have arisen from the inferior growing point. Since a dichotomy has occurred thus early, the divergence of the two groups of cells brings it about that two diverging primitive streaks are formed and thus two *anlagen* will be laid down, and in turn, the organs that arise from each *anlage* will be the duplicate of those that arise from the other.

If, however, a relatively late dichotomy of one of the growing points occurs, time enough will have elapsed for the two growing points to be separated from one another by fixed cells, which give rise to a normal primitive streak, and the dichotomy can affect only certain parts of one pole, thus:
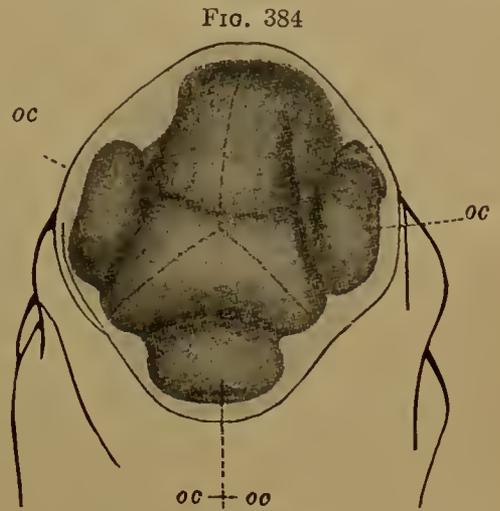
Fig. 384

Late dichotomy of superior growing point. Doubling of optic vesicles and forward part of head only of newt embryo in one of Spemann's experiments: *oc+oc*, fusion into median eye of right half of left optic vesicle with left half of right.

Dichotomy of the superior pole gives **anadidymus** and of the inferior **katadidymus**; of both, **anakatadidymus**, thus:

It happens in animals, although not yet seen in man, that the cells in the middle projected back from the respective growing points either fail to unite or become separated, thus causing **mesodidymus**, which might be indicated thus:

Finally, if the cleavage of both growing points happens very early, two parallel primitive streaks are developed side by side, giving rise to **fusional duplication**, thus:

a figure which differs from anakatadidymus in that the trunk has two complete longitudinal axes and the skeletal parts of two complete trunks.

There follows a large class of double monsters, to which the last-named division is the key; first of all, a complete cleavage has occurred, and a secondary fusion has been brought about between the parts of the body which are contiguous; the figure last given indicates the "Siamese Twins" form, but it will be understood that there are many possible modifications, as head to head, waist to waist, in an axial direction, buttock to buttock, breast to breast, and so on. Sometimes the directions of growth, and interference of tissues with one another lead to the suppression of certain organs; interesting as this subject is, it is scarcely in place in this volume. Possibly the strangest of these monsters is the **janiceps**, in which, as one looks at the monster,

FIG. 385 FIG. 386

Apicopolar fusion: disymmetrical Janiceps (Cephalothoracopagus disymmetros (Schwalbe's case). The two secondary front or facial aspects are absolutely similar.

one sees a rather toad-like figure, with a face, two arms, and two legs; if one walks around it one sees on the other side an exactly similar face, two arms, and two legs (Figs. 385 and 386). It is to be noted that such fused monsters may be equal, or unequal, in size, until the inequality becomes so marked that one has its frame "parasitic" upon the other, the so-called **teratoid**.

Duplication of Organs.—Just as there is cleavage of the axial growing points there may be cleavage, also, of the secondary growing points, which ordinarily give rise to the limbs, so that abnormalities of these arise.

These abnormalities of excess may arise in (1) longitudinal series and (2) lateral series. Excess in longitudinal series is shown by the development of extra vertebræ, or extra ribs; extra vertebræ need not have extra ribs nor need extra ribs arise from extra vertebræ; the ribs even may show excess in lateral series, when for example, the sternal end is

bifid. Excess in lateral series is oftenest exemplified by **polydactyly,** in all grades from a double nail to an accessory digit; polymastia (increased number of breasts), and duplication of internal organs are familiar examples of this abnormality. Accessory organs may exist by

Fig. 387

Fig. 388
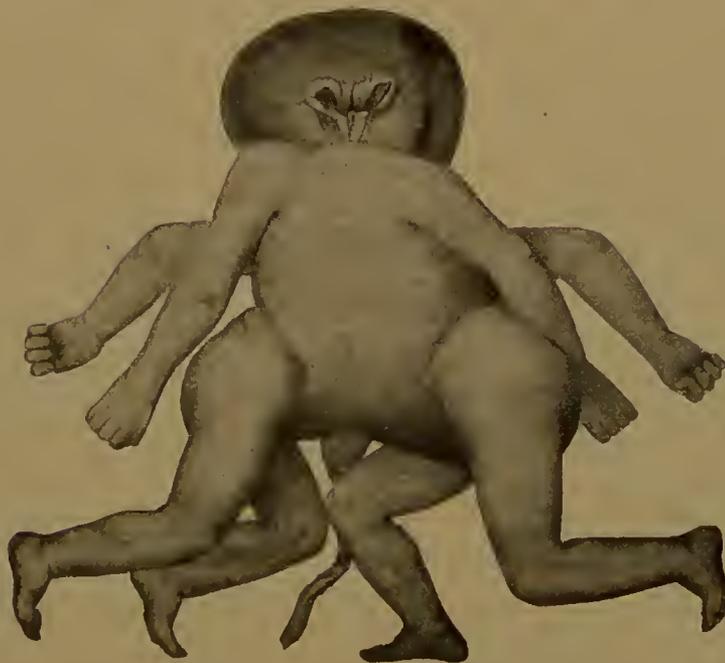
Apicopolar fusion at an angle less (or greater) than 180 degrees. Monosymmetrical Janiceps (Cephalothoracopagus monosymmetros) (Vrolik's case): Fig. 387, the perfect secondary front view; Fig. 388, the defective secondary front view, with synotia (fusion of ears).

true duplication, but more often this is due to segregation of certain cells from the rest of the organ, which develop in some situation often quite remote from the original organ. The spleen and the adrenal furnish the most frequent examples of this.

Abnormalities of Defect.—Just as giantism is the expression of a general abnormality of excess, **dwarfism** is that of a general abnormality of defect. The minimum height of normal may be given as 4 feet, 11 inches, below which there will be a number of individuals who are dwarfs by the operation of the law of chance. As with giantism, so with dwarfism, inherited disturbances of some of the ductless glands appear to be factors in the production of a certain number of cases.

Defect in Organs or Special Regions.—This may be due to (1) hypoplasia, where an organ is small merely by relative poverty of the amount of matrix

Fig. 389

Thoracic parasite (Gastrothoracopagus parasiticus). (Wirtensohn.)

Fig. 390

Cyclops proper, with median single orbit and pupil. (After Ahlfeld.)

Fig. 391

A

B
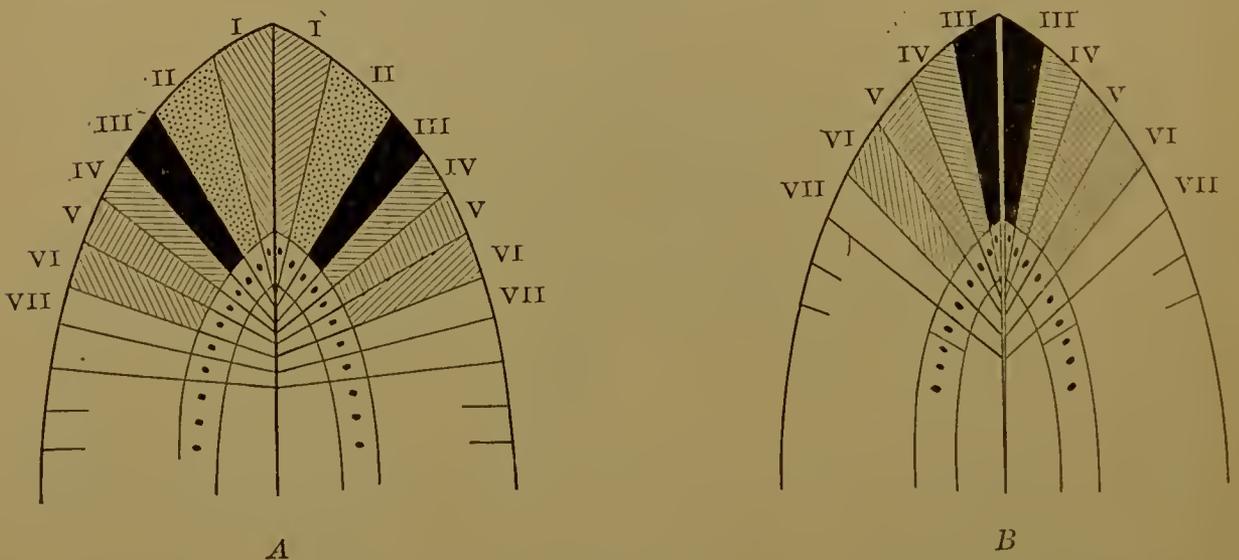
Diagram to illustrate mode of production of polar hypogenesis: *A*, the normal development of the apical portion of the organism, the daughter cells given off by the growing point controlling the development of the apical parts of the body; *B*, premature exhaustion of the growing point cells, those controlling segments *I* and *II* not being developed. As a consequence, segments *III* meet in the middle line.

set apart for that organ; or to (2) polar hypogenesis, which is the opposite of dichotomy. Just as excess at the growing point is manifested by a dichotomy, and the existence of two growing points, instead of one, so defect at the growing point may result in cessation of its growth, a premature dying out of growth; at the superior pole, if the growing point die out, and the cells behind are constantly pushing it forward, and there is no new growth of cells in the middle to keep the lateral parts away from one another, they never leave their state of approximation, and it may thus happen that two eyes from this absence of intermediate parts may fuse into one (various grades of **cyclops**), or even that no facial parts develop at all.

Similarly, at the inferior pole we may find a series of defects, which in its simplest form is seen as defect or absence of genitalia, and in its more extreme grades, fusion of the lower limbs or even the representation of the lower limbs by a fused footless stump (**sympus apus**). By a similar defect in lateral growing points, arises **syndactyly** (fusion of fingers) or reduction in the number of digits.

FIG. 392

Sirenomelus. (Sympus apus, Förster.)

FIG. 393
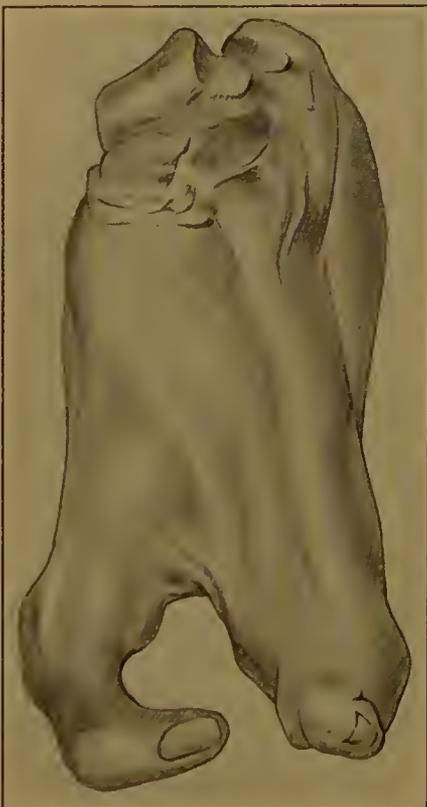
FIG. 394

Claw-foot. An abnormality of defect, which has a tendency to be familial. Note that the tarsus and metatarsus are both affected.

Local Malformations.—Imperfect Closure of the Dorsal Groove.— The neural canal originates as a longitudinal depression in the epiblast, the epiblast lining the depression being differentiated into neuroblast, which is the precursor of the nerve tissue. When the heaped-up edges of this depression meet one another they enclose the neural canal, as if the banks of a ditch overhung it more and more until they met over it. At times, this closure fails, either throughout the whole length or in some part of it. If the failure to close be at the head, the vault of the skull and the scalp are absent, and there is exposed congested tissue which appears like a mass of vascular membranes. This constitutes **anencephaly, acrania,** or **hemicephaly.** It has been supposed that pressure upon the head by amniotic adhesions at an early period causes some of these cases; parental infection in others is the basis for this vicious development. With such cranial defect there is often associated a failure in the closure of the spinal canal proper—the so-called spina bifida. **Exencephaly** is the condition in which, while the frontal region of the skull may be developed, though receding, the imperfect brain hangs out through the back of the skull. In **iniencephaly** the occipital bone is deficient and the spine bifid, so that part of the brain projects while the occiput and the sacrum are approximated, the body being bent backward.

When the laminæ of vertebræ fail to unite the condition is called **spina bifida;** clinically, the important point in this is to know to what extent the spinal cord is involved in the defect. Cases of spina bifida may be classified as follows:

1. *Complete Spina Bifida.*—Here the groove fails to close and the superficial layer of nerve tissue is continuous with the skin on each side, lying as a broad plate. If only a small part of the canal be thus open, the condition is compatible with life until the canal becomes infected or until so much fluid is drained away that the child dies.

2. *Incomplete Spina Bifida.*—Here there is failure of the bony structures, but the skin covers the protrusion or the gap. This form is classified as meningocele, myelocele, meningomyelocele, syringomyelocele, and the least serious form known as **spina bifida occulta.** The definition of these forms may be left with surgical text-books.

Imperfect Closure of the Anterior Body Surface.—The embryo is at first flat, spread out over the surface of the ovum, and with time the edges curve in to meet, forming the body cavity. For some time this closure does not take place and the viscera actually protrude, as does the allantois. The union ultimately may be incomplete, and according to the region in which failure occurs, we have:

1. *Sternal Fissure.*—If the defect of closure be complete the thoracic viscera protrude; if the lungs do so, they cannot expand, and birth is death. If the heart alone be left exposed, **ectopia cordis** results.

2. *Abdominal Fissure.*—This causes eventration, the protrusion of the viscera.

3. *Hernia of the Umbilical Cord.*—An incomplete closure of the wall at the umbilicus may result in the proximal part of the cord being

enlarged to receive a portion of the viscera. A condition not unlike this arises when the omphalomesenteric duct, which originally connects the gut and the yolk sac, remains open.

4. *Vesicogenital Fissure.*—The allantois develops from the hind gut and runs through the umbilical region; the part nearest the urogenital

Fig. 395
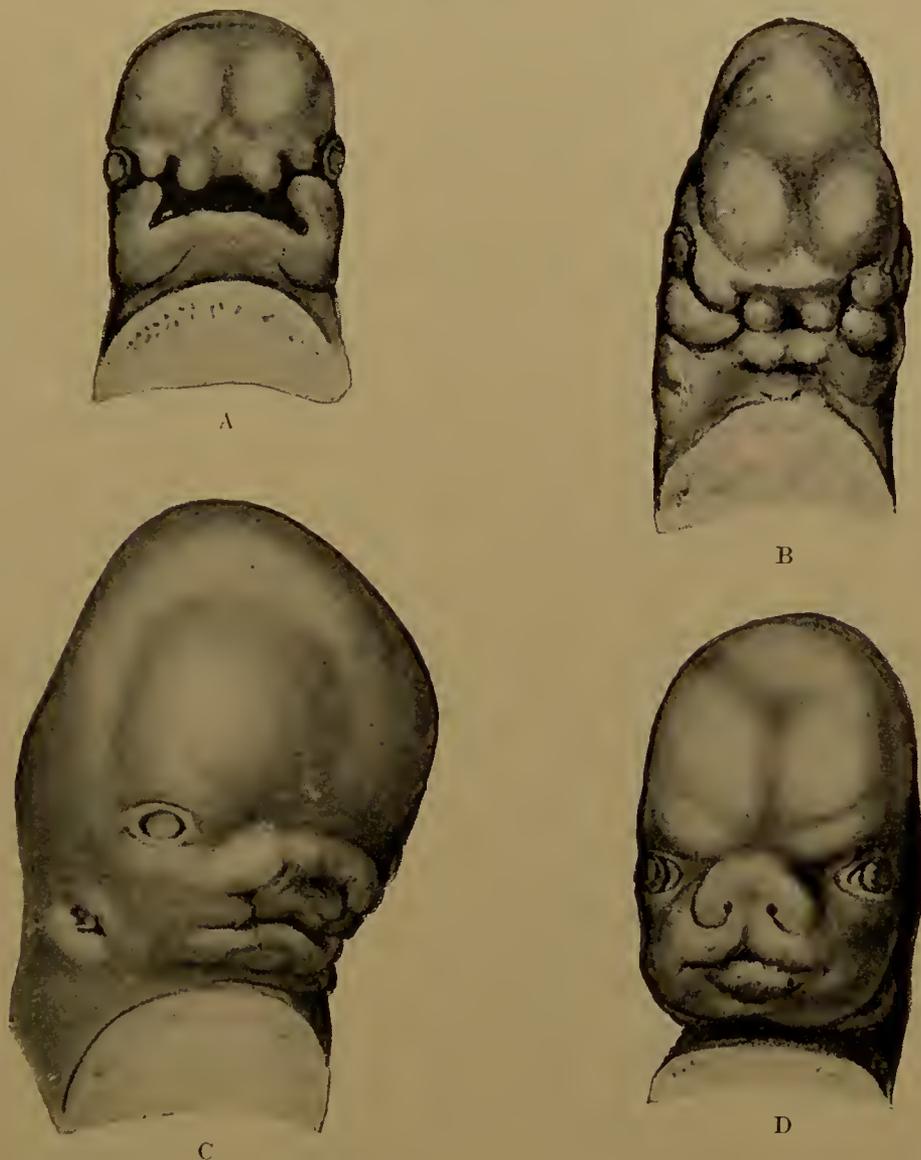
Development of the face of the human embryo (His): *A*, embryo of about twenty-nine days. The nasofrontal plate differentiating into processus globulares, toward which the maxillary processes of first visceral arch are extending; *B*, embryo of about thirty-four days; the globular, lateral frontal, and maxillary processes are in apposition; the primitive opening is now better defined; *C*, embryo of about the eighth week: immediate boundaries of mouth are more definite and the nasal orifices are partly formed, external ear appearing, *D*, embryo at end of second month. (Heisler.)

sinus widens into the bladder, and the part distal to this closes, and extends as a cord (urachus) to the umbilicus. The urachus may fail to close, and may remain as a tube; the bladder may fail to close, constituting **ectopia vesicæ**. Associated or not with this, the urethra may fail to close being represented by, at most, a *dorsal* groove upon the penis or clitoris, constituting **epispadias**.

Imperfect Closure of the Facial Clefts.—The accompanying diagram will remind the reader of the different fusions that occur, with obliteration of clefts, when the face is formed. When the fusion of these apposing surfaces is inhibited totally or in part, we have produced the features of an earlier developmental stage. Of such failures, **harelip** in its various degrees, with the accompanying palatal malformations, is the one of most clinical interest. In its simplest form, harelip affects only one side of the upper lip; a severer form is that in which, in addition, there is a lack of union between the maxillary process and the intermaxillary bone extending into the hard or the hard and soft palate —**cleft palate**—or this may occur on both sides—*double cleft palate;* or the intermaxillary bone may be wanting—*median cleft palate;* or externally, the cleft may extend along the side of the nose to the orbit.

Imperfect Closure of the Branchial Clefts.—In the embryo the second and lower branchial clefts pass from the outside into what ultimately will be the pharynx. If one of these do not close at all, a complete fistula remains; if it close at the end, a sinus is made, and if it close at both ends a cyst; if the cyst be formed from the part of the cleft nearer the skin, its epithelial lining is squamous, if from the pharyngeal end, columnar and even ciliated. The Eustachian tube is the first of these clefts, of which there are five; the second is the one which oftenest persists.

Rectal Malformations.—The embryonic cloaca in the course of development is transformed into certain external genitalia and the rectum. If the separation between the genital and the rectal parts do not occur, we have the condition of **persistent cloaca**; if it occur only partially, a fistula is formed, the cavity of the rectum communicating with some part of the genito-urinary tract, such as the vagina, the bladder or the urethra. Also, the septum between the hind gut and the outside may not be broken down, and the condition of **atresia ani** or imperforate anus may result. There are various grades of this, according to the distance from the surface at which the end of the hind-gut lies.

Hermaphroditism.—The matrix tissue (*anlage*) of the genitalia remains the same in the two sexes up to the fifth week, and alike structures become transformed into the apparently widely differing organs found in the two sexes. Each part of the male tract has thus an analogue in the female. It is not so strange that cases of blended sex should occur, as that they should occur so rarely.

True Hermaphroditism.—This is very rare; there may be an ovary on one side and a testis on the other, or both on one side, and either or neither on the other, or finally, both on each side. The secondary sexual characters (the conformation of the body and its parts) are mixed.

False Hermaphroditism.—This is far more common than the former. In it the genitalia are actually of one or the other type, but the secondary characters are those of the sex other than that to which the genitalia belong. The male individual with feminine characteristics is the more common of these (**pseudohermaphrodismus masculinus**).

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